Faculty of Medicine
University of Helsinki

ISCHAEMIC DIABETIC FOOT

PERSPECTIVES ON LONG-TERM OUTCOME

Milla Kallio

DOCTORAL DISSERTATION

To be presented for public discussion, with the permission of the Faculty of Medicine of the University of Helsinki, in Auditorium 1, Metsätalo, on the 14th of August, 2020 at 12 noon.

Helsinki 2020

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ISBN978-951-51-6295-3(nid.)
ISBN 978-951-51-6296-0 (PDF)

Unigrafia
Helsinki 2020

To individuals who live or work with chronic ulcers

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ORIGINAL PUBLICATIONS

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Kallio M, Forsblom C, Groop PH, Groop L, Lepäntalo M. Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. Diabetes Care 2003; 26:1241-1245.

II

Tukiainen E, Kallio M, Lepäntalo M. Advanced leg salvage of the critically ischemic leg with major tissue loss by vascular and plastic surgeon teamwork: Long-term outcome. Ann Surg 2006; 244:949-957; discussion 957-958.

III

Kallio M, Vikatmaa P, Kantonen I, Lepäntalo M, Venermo M, Tukiainen E. Strategies for free flap transfer and revascularisation with long-term outcome in the treatment of large diabetic foot lesions. Eur J Vasc Endovasc Surg 2015; 50:223-230

IV

Kallio M, Lepäntalo M, Venermo M. The 10-year outcome of a prospective cohort of diabetic and non-diabetic patients with ischemic ulcers. Submitted.

ABBREVIATIONS AND DEFINITIONS

ABI	ankle-brachial index
AFS	amputation-free survival
ADP	arteria dorsalis pedis
AMI	acute myocardial infarction
ATA	arteria tibialis anterior
ATP	arteria tibialis posterior
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CLI	critical limb ischaemia
CLTI	chronic limb-threatening ischaemia
cm	centimetre
CRP	c-reactive protein, an inflammatory marker
CTA	computed tomography angiogram
DM	diabetes mellitus
DFU	diabetic foot ulcer
DSA	digital subtraction angiography
EBR	evidence-based revascularisation
ESRD	end-stage renal disease
FTT	free tissue transfer
GLASS	Global Limb Anatomic Staging System
HDL	high-density lipoprotein
HLA	human leucocyte antigen
HR	hazard ratio
IDF	International diabetes federation
IQR	interquartile range
IWGDF	International Working Group for Diabetic Foot
LEAD	lower extremity arterial disease
LD	latissimus dorsi

LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MALE	major adverse limb event
MRA	magnetic resonance imaging
MW	Meggit-Wagner
NHS	National Health Service (UK)
NPWT	negative-pressure wound therapy
OR	odds ratio
PAD	peripheral arterial disease
PLAN	patient risk estimation, limb staging, anatomic pattern of disease
PTA	percutaneous transluminal angioplasty
PVR	pulse volume recording
RR	risk ratio
STSG	split-thickness skin graft
SSGSV	single-segment great saphenous vein
$tcpO_2$	transcutaneous oxygen pressure
TASC	Trans-Atlantic intersociety consensus
TAP	target artery pathway
TAP	thoracodorsal artery perforator
TIA	transient ischaemic attack
TMT	transmetatarsal
TP	toe pressure
UK	United Kingdom
US	United States
UT	University of Texas
WHO	World Health Organisation

ABSTRACT

Background: Diabetes increases the risk of major amputation 7.6-fold compared to the nondiabetic population in Finland. The risk of amputation is highest in patients with ischaemia and an infection. While efforts are being made for the better prevention and early identification of ulcers, understanding ischaemic ulcers and their treatment, even the most complicated ones, is still necessary.

Aim: We aimed to study lower extremity arterial disease (LEAD) and its risk factors in a cohort of type 2 diabetic patients, in addition to investigating the long-term outcome of patients with ischaemic diabetic foot tissue defects according to the mode of treatment.

Patients and methods: 130 type 2 diabetic patients, arbitrarily selected from the register of the Helsinki Diabetes Association, were examined at baseline in 1983–1985 and 93 available patients at follow-up an average of 11 years later. Ankle-brachial index (ABI) and serum and urine tests were taken at baseline and ABI again at follow-up (Study I). Data on all free tissue transfer (FTT) operations for diabetic and ischaemic tissue defects of the lower extremities from the beginning of operations in Helsinki in 1989 to 2003 were collected mainly from medical records (Studies II and III). Ninety-nine consecutive patients admitted for angiography due to a suspicion of an ischaemic ulcer were examined and interviewed in 1999 (Study IV). Long-term outcome was analysed mainly based on follow-up data from medical records and, in Study I, based on a new measurement of (ABI).

Main results: At baseline, LEAD in type 2 diabetic patients was associated with age, the duration of diabetes, smoking and the urinary albumin excretion rate. The development of new LEAD 11 years later, after the death of the most morbid group of patients, was associated with low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol levels. (Study I.)

After combined FTT and vascular reconstruction, the postoperative period was uneventful only in 22% of the patients. The one- and five-year limb salvage rates were 73% and 66%, survival rates 91% and 63%, and amputation-free survival rates 70% and 41%, respectively. Fifty-two percent of the patients were able to ambulate with the preserved leg at two years. Minor ulcer recurrence was observed in 54% of the patients with primary skin healing. (Study II.)

In diabetic patients, the amputation-free survival (AFS) rates at one, five and ten years were 90%, 79% and 63%, respectively, among those not requiring revascularisation; 66%, 25% and 18%, respectively, among those who underwent revascularisation; and 50%, 42% and 17%, respectively, among those with uncorrectable ischaemia. Major

amputation was associated with smoking, heel ulceration, nephropathy and an ulcer diameter of over 10 cm. (Study III.)

Of the patients with ischaemic ulcers, 75% underwent revascularisation, whereas the remaining 25% received conservative treatment. Of patients who underwent revascularisation, 7 had type 1 diabetes and 33 type 2 diabetes, and 31 were non-diabetic. The one-, five- and ten-year AFS rates in the whole cohort were 59%, 31% and 11%, respectively. In multivariate analysis, amputation during the first year of follow-up was significantly associated with unreconstructable ischaemia, uraemia and elevated CRP (c-reactive protein). (Study IV.)

Conclusions: A low ABI predicts cardiovascular mortality in diabetic patients with no other signs of cardiovascular disease. Smoking, urine albumin excretion rate, LDL cholesterol and HDL cholesterol are modifiable factors that should be addressed in order to decrease the risk of LEAD.

After FTT excellent AFS at five years can be expected in diabetic patients with a native artery open to the foot. Even in the absence of options for revascularisation, moderate AFS can be achieved with careful individual assessment. A large ulcer size and location in the heel were associated with amputation after FTT – in diabetic patients also smoking and uraemia.

In patients with ischaemic ulcers, the amputation rate was high during the first two years of follow-up, and mortality was high during the whole follow-up period; the 10-year AFS was 11%. Amputation during the first year was independently associated with elevated CRP, uraemia and uncorrectable ischaemia. Ulcer healing was similar in nondiabetic (65%) and type 2 diabetic patients (67%) with revascularisation.

1 INTRODUCTION

A foot ulcer is a serious complication of diabetes. Major amputations in diabetic patients are in 85% of the cases preceded by ulceration (Larsson et al. 2008, Reiber et al. 1998, Singh et al. 2005). Diabetes increases the risk of major amputation 7.6-fold compared to the nondiabetic population in Finland (Ikonen et al. 2010). Ulcers also decrease the mobility of patients, restrict their social life, require resources for ulcer care and cause hospitalisations. Moreover, diabetic foot ulcers are independently associated with mortality (Martins-Mendes et al. 2014). In diabetic patients, three important aetiological factors of chronic ulcers are ischaemia, neuropathy and infection. Neuropathy is present in roughly 90% of ulcers and ischaemia in 50% (Prompers et al. 2007) .The risk of amputation increases in patients with ischaemia and an infection, and it is very high in patients with both of these conditions (Prompers et al. 2008).

The prevention of ulcers is possible in many ways. Optimal glucose balance, the avoidance of atherosclerosis risk factors, as well as foot care and educating patients and professionals may prevent the majority of ulcers and ward off the deterioration and non-healing of upcoming ulcers. A careful foot examination is an important part of a routine check on diabetic individuals, as is education on foot care and the prevention of foot problems.

When a tissue lesion exists, the identification and timely treatment of ischaemia is of utmost importance for the outcome of diabetic foot ulcers. The diagnosis of peripheral arterial occlusive disease in diabetic patients is challenging due to the often sclerotic medial layer of the artery that results in falsely high ankle pressures. Hence, routine toe pressure measurements and low-threshold imaging studies are recommended. Due to neuropathy, patients may not feel pain, and the tissue lesion is often already extensive when a patient seeks help. In neuroischaemic ulcers, the correction of ischaemia with srevascularissation is mandatory to achieve wound healing. When a tissue lesion affects the joints, tendons and even bone, extensivesischaemia plastic surgery is needed to cover the tissue lesion in addition to correcting the ischaemia by means of revascularisation.

At present, the number of diabetic patients is growing, while prevention as well as early intervention remain only halfway towards being fully implemented. Understanding ischaemic ulcers and their treatment, even the most complicated ones, is necessary. The objective of the present thesis was to study peripheral arterial disease and foot ulcers in diabetic patients and, further, the treatment of extensive diabetic foot ulcers.

2 REVIEW OF THE LITERATURE

2.1 DIABETES MELLITUS (DM)

2.1.1 DEFINITION

The term diabetes mellitus (DM) covers a state of chronic hyperglycaemia induced by a deficiency in insulin production or by a decreased sensitivity to insulin caused by multiple aetiologies. The global criteria for the diagnosis of diabetes were published and updated by the World Health Organisation in 1965, 1980, 1985, 1999 and 2006 in collaboration with the International Diabetes Association. (WHO 2006). In 2011 the WHO recommended glycated haemoglobin as an additive test, and the International diabetes federation (IDF) global guideline from 2012 named any one of the following as a diagnostic test: fasting plasma glucose, oral glucose tolerance test, glycated haemoglobin or random plasma glucose (WHO 2011, IDF 2012). In Finland, a national guideline, the Current Care Guidelines on Diabetes, first published in 2007, follows the international guidelines (Type 2 diabetes Current Care Guidelines 2018, Insulin deficiency diabetes. Current Care Guidelines 2018).

A recent guideline by the WHO names a diversity of diabetes types. The classical main types, type 1 and type 2, are still valid (WHO 2019). In the past, the terms insulin-dependent diabetes (IDDM) or juvenile-onset diabetes for type 1 diabetes, and non-insulin-dependent diabetes (NIDDM) or adult-onset diabetes for type 2 diabetes, were used. Subtypes of these two forms have been replaced by a hybrid form of diabetes containing characteristics of both two main types. Type 1 and type 2 diabetes have classically been differentiated by the age at diagnosis and the need for insulin. However, instead of a strict division to these two main types, a continuum from insulin resistance to insulin deficiency corresponds with the current view where the disease may shift from one type to another. Therefore, unclassified diabetes has been newly introduced into the classification. Other main categories are specific types of diabetes, including monogenic diabetes types, and diabetes first detected during pregnancy (WHO 2019). The American Diabetes Association cites gestational diabetes and a specific type of diabetes due to other causes in addition to type 1 and type 2 diabetes (American Diabetes Association 2019).

2.1.2 AETIOLOGY

The two main types of diabetes both have a genetic predisposition, which is more pronounced in type 2 diabetes. While an identical twin of a patient with type 1 diabetes has a 30%–50% risk of the disease, the risk for a twin of type 2 diabetic is over 50%

(Olmos et al. 1988, Kerner et al. 2014). However, environmental factors are a requisite for the expression of the disease. Moreover, type 1 and type 2 diabetes display heterogenic aetiologies, many of which are unknown at present (Flannick et al. 2016, American Diabetes Association 2019, WHO 2019).

Type 1 diabetes occurs when an autoimmune process destroys the beta cells of the pancreas. Very active research is under way regarding the aetiology of type 1 diabetes. Autoantibodies to islet cells, insulin, Glutamic Acid Decarboxylase (GAD) and to thyroxine phosphatase are detectable at the time of diagnosis in over 85% of patients with type 1 diabetes. Linkage to certain human leucocyte antigen (HLA) genotypes is frequent as well. (American Diabetes Association 2019.) A strong role of environmental factor seems evident. Enterovirus infection is at least one of the candidates (Blanter et al. 2019).

Type 2 diabetes is often linked to metabolic syndrome, obesity and reduced mobility. Genetics are important, but the exact mechanisms remain poorly defined. It seems that the genetic network is very complicated, and type 2 diabetes in particular has connections with various monogenic diabetes types that have recently been recognised due to new methods available in genetic research.

2.1.3 EPIDEMIOLOGY

The incidence of type 2 diabetes is increasing throughout the world.

The highest numbers of diabetics live in China (98 million), India (65 million) and the United States (US) (24 million) due to the vast populations. However, the highest prevalence of diabetes is observed in some Middle Eastern countries as well as on the Western Pacific Islands, where the comparative prevalence (corrected by age) of diabetes lies between 23% and 37%. The estimated global comparative prevalence in 2019 was 9.3%. (IDF 2019.)

The national prevalence of diabetes in Finland is 9.2% (95% CI (confidence interval) 6.7–11.5), and the comparative prevalence is 5.6% (95% CI 4.0–7.4) (IDF 2019). Based on the statistics of the Social Insurance Institution of Finland (KELA), 320 000 persons purchased diabetes medications in 2011. According to the IDF data, the number of diabetic persons is 350 000. As undiagnosed diabetes is frequent and not all diabetics need medication, the estimated number is over 500 000 diabetic patients (Finnish Institute for Health and Welfare 2020).

In Finland, 75% of diabetic patients have type 2 diabetes (Type 2 diabetes. Current Care Guidelines 2018), whereas 90%–95% of the American diabetic population have type 2 diabetes (American Diabetes Association 2019). In contrast, type 1 diabetes is diagnosed in 15% of diabetic patients in Finland and in 5%–10% in the US (Insulin deficiency diabetes. Current Care Guidelines 2018, American Diabetes Association 2019).

Finland has the highest incidence of type 1 diabetes in the world (IDF 2019). The mean incidence of type 1 diabetes in Finland was 62.5 (95% CI, 60.2–64.4*)* per 100 000 person-years between 2006 and 2011 in children younger than 15 years of age (Harjutsalo et al. 2013). The IDF estimate of type 1 diabetes incidence among children under 15 years of age was 62.3/100 000 for 2015 (IDF 2015).

The prevalence of diabetes is remarkable in older age groups. In a population-based survey in Wales, the overall prevalence of diabetes was 3.4% in 2004. As regards the older population, the prevalence was 7.7% in men and 5.6% in women between 55 and 64 years of age, 13.6% in men and 9.6% in women between 65 and 74 years, 13.9% in men and 9.8% in women between 75 and 84 years, and 17.9% and 12.1% in men and women, respectively, over 85 years of age (Morgan et al. 2010).

2.1.4 DIABETIC COMPLICATIONS

Diabetes mellitus leads to microvascular and macrovascular complications, which significantly reduce the quality of life and cause huge costs. The microvascular complications comprise nephropathy, retinopathy and neuropathy, while the macrovascular complications include atherosclerotic diseases, such as coronary artery disease, cerebrovascular disease and peripheral arterial disease. These complications also predispose diabetic patients to chronic ulcerations or may affect the prevention and treatment of ulcers

In high-income countries, the incidence of macrovascular complications is decreasing due to better cardiovascular risk factor and blood glucose control, an earlier detection of diabetes, better organisation of care and better self-management. As the decrease has been steeper than in the population without diabetes, the excess risks of such complications for diabetic patients are no longer so striking. An analysis based on the Swedish national registry observed a 26% excess in all-cause mortality among diabetic population when compared to the nondiabetic population in 1998–2011 (Tancredi et al. 2015).

In older patients, the relative risk of macrovascular complications has decreased compared to the younger age groups. It has been speculated that the complications will be diversified in the future as people with diabetes live longer in the absence of macrovascular complications. Deaths due to cancers, renal disease, mental and physical disability as well as the cardiovascular complications peripheral vascular disease and heart failure may become more common. (Gregg et al. 2016.) The decrease in microvascular complications has been less notable. In the US, nephropathy, and probably retinopathy, decreased by half the rate of macrovascular complications (Gregg et al. 2016).

The incidence and prevalence of complications is different in type 1 and type 2diabetes. The numbers are influenced by age, age at diabetes onset and disease duration. The

type 1 diabetic population in general is younger, the diagnosis is made at a notably younger age, and the disease duration is longer than in the type 2 diabetic population. Recently, however, the number of young-onset type 2 diabetes patients has been increasing. A comparison of type 1 and type 2 diabetic patients of the same age of onset reveals that the prognosis of type 2 diabetics seems less favourable. Macrovascular complications and mortality have been found to be higher in type 2 compared to type 1 diabetes after an over 20-year follow-up (Constantino et al. 2013). The rates of some type 1 diabetes complications (mortality, renal failure and neuropathy) are declining. However, others (coronary artery diasease, overt nephropathy and proliferative retinopathy) show less favourable changes by 30 years (Pambianco et al. 2006)

2.1.4.1 NEPHROPATHY

Microalbuminuria is an easily measurable early sign of diabetic nephropathy. Microalbuminuria is observed in 20%–30% of type 1 diabetic patients 15 years after the onset of diabetes (Hovind et al. 2004). One in five of type 2 diabetic patients has microalbuminuria at onset and one in three after ten years (Adler et al. 2003). The prevention of the progression of microalbuminuria to macroalbuminuria and elevated creatinine values, in both type 1 and type 2 diabetes, includes good glucose and blood pressure control and the elimination of other risk factors**.**

End-stage renal disease (ESRD) represents the most severe stage of renal insufficiency. The kidneys excrete excess fluids and harmful substances insufficiently. This leads to the need of dialysis treatment. Based on existing studies from different countries, 12%–66% of patients with ESRD have diabetic nephropathy (Gregg et al. 2016).

In Finland, after a diagnosis of type 2 diabetes, the 10-year cumulative risk of developing ESRD has been found to be 0.29% and 20-year risk 0.74% (Finne et al. 2019). After a diagnosis of type 1 diabetes, the cumulative incidence of ESRD has been reported to be 2.2% at 20 years and 7.8% at 30 years. ESRD was rare within the first 15 years after the diagnosis of type 1 diabetes, but the incidence increased thereafter. The risk of ESRD was lowest in those with the onset of DM (diabetes mellitus) occurring before the age of 5 years. (Helve et al. 2018.) In Finland, type 2 diabetes is the most frequent diagnosis in patients undergoing haemodialysis. However, type 1 diabetes just surpassed type 2 diabetes as the most frequent diagnosis in the background of the initiation of active treatment for ESRD. Type 1 diabetes was the most frequent diagnosis in those who receive peritoneal dialysis (Finnish Registry for Kidney Diseases 2017).

Renal transplantation can normalise the renal function. Type 1 diabetes is the third most frequent diagnosis among patients receiving a renal transplant. Among renal transplant recipients, type 2 diabetes is a relatively rare diagnosis (Finnish Registry for Kidney Diseases 2017).

The mortality rate is high among diabetic patients with ESRD. In Finnish type 2 diabetic patients, the ten- and 20-year cumulative risk of death was 34% and 64%, respectively. ESRD increased the risk of death 4.2-fold (Finne et al. 2019). In a large health maintenance organisation in the US, 46% of uraemic patients died and only 18% were initiated on dialysis. Diabetic patients were overrepresented among those who died, as were patients with congestive heart failure, coronary artery disease or anaemia. (Keith et al. 2004.) In another study on patients with type 2 diabetes, the prevalence of microalbuminuria ten years after diagnosis was 25%, of macroalbuminuria 5.3% and of permanently elevated creatinine levels or renal replacement 0.8%. Notably, for a patient with macroalbuminuria, death was more probable than developing more severe nephropathy. The annual mortality rate was 3.5% in patients with macroalbuminuria and 12% in patients with elevated creatinine levels or renal replacement therapy. (Adler et al. 2003.)

2.1.4.2 RETINOPATHY

Retinopathy affects patients with DFU (diabetic foot ulcer) in at least in two ways. Visual impairment hinders self-surveillance of the feet. Retinopathy is associated with an increased risk of LEAD in type 1 diabetics (Pongrac Barlovic et al. 2018). According to the current understanding, the pathologies underlying diabetic retinopathy are damage to the neural retina and the capillary vascular bed of the retina. The clinical manifestations are proliferative retinopathy and macular oedema. Retinopathy can be prevented or delayed with a good control of glucose and lipid balance, as well as blood pressure. The clinical disease can be treated with laser and vitreous anti-vascular endothelial growth factor (VEGF) medication injections (Shah and Gardner 2017). Screening and early treatment were shown to reduce visual impairment in a population-based study with both type 1 and type 2 diabetic patients (Hautala et al. 2014). Without proper treatment, diabetic retinopathy may lead to visual loss (Shah and Gardner 2017). Approximately one third of diabetic patients develop retinopathy. The prevalence of retinopathy among individuals with a diagnosis of diabetes varies from 10% in Norway to 61% in Southern Africa; in many countries, including Finland, these data are not available (IDF 2012). In an Australian study, the prevalence of retinopathy was 21.9% among those with known type 2 diabetes and 6.2% among those with newly diagnosed type 2 diabetes (Tapp et al. 2003).

The incidence of retinopathy is probably declining, based on the few existing studies, which are not yet specific for retinopathy. In a study from the US, self-reported visual impairment decreased from 27% to 19% between 1997 and 2012 (Gregg et al. 2014). In Finland, the incidence of retinopathy requiring laser treatment is declining (Kytö et al. 2011).

In type 1 diabetes, retinopathy rarely occurs during the first five years after diagnosis or before adolescence (Insulin deficiency diabetes. Current Care Guidelines 2018). In a

cohort of type 1 diabetic patients, the 20-year cumulative incidence of severe retinopathy was 18% (Kytö et al. 2011).

2.1.4.3 NEUROPATHY

In addition to foot problems, neuropathy increases morbidity in diabetic patients in the form of pain, as well as gastrointestinal and urinary tract problems, and it is associated with increased mortality (Ziegler et al. 2014). Patients and health care personnel alike are often unaware of the presence of polyneuropathy (Ziegler et al. 2015).

Two aetiologic factors have been named for diabetic polyneuropathy (DPN): the number of nerve fibres is diminished and the microvasculature of the nerves is injured. On the background are metabolic abnormalities (Tesfaye and Selvarajah 2012). Age, the duration of diabetes, the height of the patient and uric acid have been associated with neuropathy (Tapp et al. 2003, Young et al. 1993). Peripheral neuropathy is also associated with peripheral arterial disease (Ziegler et al. 2015, Ylitalo et al. 2011). In one study, ENMG-confirmed neuropathy was observed in 73% of 30 diabetics with at least one significant stenosis or occlusion in the iliac, femoral or popliteal artery (Kim et al. 2014).

Many subtypes of neuropathy and an almost endless list of diagnostic methods, scores and symptoms pose challenges as regards comparisons between epidemiologic studies. According to a review article, diabetic sensory polyneuropathy (DSPN) affects less than 20% of the diabetic population identified by screening. The prevalence was 13%–23% in a hospital-based material of type 1 diabetics and 18%–75% among type 2 diabetics. In a population-based and primary care cohort, the prevalence of DSPN was 8%–63% among type 1 diabetic patients and 13%–51% among type 2 diabetic patients. The prevalence based on nerve conduction velocities was higher: 29%–75%. (Ziegler et al. 2014.)

In studies with more accurate testing of DNP, the prevalence has been higher among type 2 than type 1 diabetic patients, and the prevalence increased with age. In a cohort of 80 type 1 and 544 type 2 diabetic patients, neuropathy was tested by means of vibration and temperature perception, as well as monofilament testing. Thirty-six percent of the type 1 diabetic patients (mean age 59 years) and 56% of the type 2 diabetic patients (mean age 69 years) had neuropathy. Of these, 5% and 8% had severe, and 30% and 30% possible neuropathy, respectively (Ziegler et al 2015). In another study, where neuropathy was assessed by pin prick and ankle reflex testing, in addition to temperature and vibration perception testing, DNP was observed in 5% of diabetic patients aged 20–29 years and in 44% of those aged 70–79 years (Young et al. 1993). In an Australian population-based study, 13.1% of participants with previously known diabetes and 7.1% of newly diagnosed diabetic patients had peripheral neuropathy,

assessed by means of temperature perception, monofilament, pin prick, vibration perception, and blood pressure drop testing combined with a symptom inquiry. The mean age of patients with neuropathy was 73 years and of non-neuropathic patients 62 years (Tapp et al. 2003).

The incidence of DNP increases with the time from the diagnosis of diabetes. In newly diagnosed type 2 diabetic patients with no neuropathy at baseline, the annual incidence of neuropathy has been reported to be approximately 2%, whereas in patients with a longer history of diabetes, the reported annual incidence has been approximately 6%–8% in different studies. The yearly incidence of neuropathy among type 1 diabetics seems to vary between 1% and 4% but may be close to 0 or progressing much more rapidly, strongly depending on the glycaemic control and the duration of DM (Ziegler et al. 2014).

2.1.4.4 NEUROPATHY AND ULCERS

Diabetic peripheral neuropathy (DPN) makes the foot vulnerable for ulcers in many ways. The loss of sensation causes pressure, friction and sharp trauma to remain unnoticed. Motor neuropathy leads to a limited mobility of the joints, affects the proprioseptics and coordination and can alter the gait and, gradually, the anatomy of the foot. Autonomic neuropathy tends to diminish sweating, causing dry feet with easily cracking skin. It also alters the regulation of blood flow and possibly induces microvascular dysfunction as well. (Lepäntalo et al. 2011.) In a European multicentre study, 86% of the patients with diabetic foot ulcers had peripheral neuropathy. Neuropathy was diagnosed if two of the following tests were positive: monofilament testing, tactile testing with cotton wool, sharp and blunt testing, and vibration testing (Prompers et al. 2007).

2.1.4.5 MACROANGIOPATHY

Macroangiopathy is a process where the intimal layer of the artery wall thickens, the epithelium is damaged, and deposits, mostly consisting of lipids, develop in the intima. With time, these deposits or plaques often calcify. The arteries become obstructed or occluded, and plaque ruptures can occur (Leszczynska et al. 2018). The most well-known manifestations of macroangiopathy are probably peripheral arterial disease, coronary artery disease and cerebrovascular disease. Their coexistence varies between the reports (Figure 1). In a population-based register study, the most common first macrovascular manifestations in diabetic patients were peripheral arterial disease and heart failure (Shah et al. 2015). At the time of diagnosis, 23.5% of diabetic patients had at least one macrovascular comorbidity (Palladino et al. 2020). In a cohort containing

the entire diabetic population in the Basque Country, the diseases based on the hospital discharge register showed a prevalence of 11.5% for ischaemic heart disease, 7% for stroke and 2.5% for peripheral vascular disease (Alonso-Moran et al. 2014). According to a systematic review of diabetic patients who underwent revascularisation, the prevalence of coronary artery disease was 38%–59% and that of cerebrovascular disease 18%–23% (Hinchliffe et al. 2016).

The risk of myocardial infarction has been found to be 1.5 times higher in the diabetic than the non-diabetic population (Shah et al. 2015). In 1999, roughly one third of diabetic individuals in the US reported any heart disease or stroke. During 1997–2009, no clear decline was seen in the prevalence of self-reported heart disease. However, the incidence of acute myocardial infarction declined by 69% between 1990 and 2010, based on US register data. (Gregg et al. 2014.)

The incidence of stroke declined by 53% between 1990 and 2010, based on US register data (Gregg et al. 2014). The hospital-discharge-register-based prevalence of stroke was 7% among the type 2 diabetic population in the Basque Country in 2010–2011 (Alonso-Moran et al. 2014). The risk factors of macroangiopathy include diabetes mellitus, smoking, hyperlipidaemia and hypertension. In the United Kingdom (UK), the risk of a person aged 40 years with no previous cardiovascular disease of developing any cardiovascular disease by the age of 80 was 67% for diabetic men, 58% for diabetic women, 44% for nondiabetic men and 31% for nondiabetic women (Shah et al. 2015).

As is well known, a non-optimal glucose balance increases the rate of microvascular complications. The connection between glycaemic control and macrovascular disease has been more arduous to reveal. Indeed, strict glycaemic control at the onset of type 2 diabetes reduces macrovascular complications, whereas a good control later, also considering symptomatic disease, may have little effect on the macrovascular complications (Lovre et al. 2015). For every 1% increase in HbA1C, there is a 25% increase in the risk of CVD in diabetic patients (Selvin et al. 2004, Muntner et al. 2005). Furthermore, the DCCT study showed that, in type I DM patients, the risk of macrovascular complications increased along with HbA1 levels (Bebu et al. 2017). Diabetes as a risk factor, especially combined with a previous cardiovascular event, increased the risk of new cardiovascular events, fatal and nonfatal. A noteworthy fact is that peripheral arterial disease is a strong predictor of cardiovascular disease in diabetic patients – stronger than cardiac or cerebral events; an accumulation of uncontrolled risk factors in patients with LEAD may offer an explanation (Krempf et al. 2010). Diabetes predicts cardiovascular mortality in patients with both symptomatic and asymptomatic LEAD (Sigvant et al. 2016).

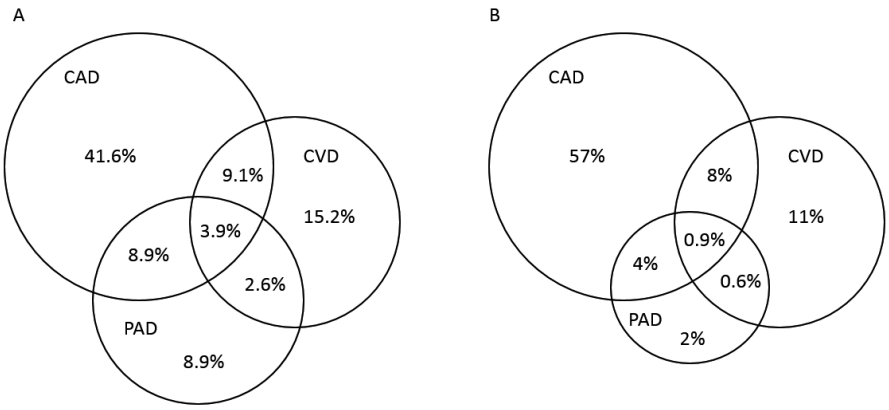

Figure 1. Presentation of cardiovascular complications in two different non-population-based study cohorts. Both diabetic and non-diabetic patients were included. A) German REACH. (Reproduced with permission from Zeymer et al. 2008). B) Canadian REACH (Reproduced with permission from Smolderen et al. 2010.)

2.2 LOWER EXTREMITY ARTERIAL DISEASE (LEAD)

Classical symptoms of atherosclerotic obstructions and occlusions in the lower extremity arteries are claudication and critical limb ischaemia, comprising rest pain and ischaemic ulcers or gangrene. However, even a multilevel occlusion often lacks symptoms, especially in diabetic patients. Indeed, in diabetic patientss with peripheral sensory neuropathy, the symptoms are typically absent, and the first symptom may be an ulcer or gangrene (Lepäntalo et al. 2011). Diabetic patients have a 2- to 4-fold risk of LEAD compared to non-diabetics (Beckman et al. 2016). With the intensive treatment of risk factors, the rate of peripheral arterial disease has been declining along with other macrovascular complications (Stratton et al. 2000, Carter et al. 2007, Selvin et al. 2004).

2.2.1 CLINICAL MANIFESTATIONS

2.2.1.1 ASYMPTOMATIC LEAD

Asymptomatic disease can be detected by noninvasive measures, such as the ABI. However, in diabetic patients, studies based on ABI measurement may underestimate the prevalence of LEAD because in 30%–50% of the cases, ankle pressure is falsely elevated due to medial sclerosis (Lepäntalo et al. 2011, Faglia et al. 2009, Acin et al.

2014, Prompers et al. 2007). According to one estimate, two thirds of all patients with LEAD are asymptomatic (Aboyans et al. 2018). In Germany, 26% of diabetic and 13% of non-diabetic individuals aged over 65 years (median age 74 years) and visiting primary care for any cause had an ABI of < 0.9 (Lange et al. 2004). In Sweden, 29% of 68-year-old men with diabetes and 12% of those without diabetes had an ABI of < 0.9 (Ögren et al. 2005). Notably, patients with asymptomatic LEAD have an increased risk of cardiovascular complications, stroke, acute myocardial infarction and death (Sigvant et al. 2016).

2.2.1.2 CLAUDICATION

Claudication is ischaemic pain that starts when the muscles of the lower extremity are exercised, typically when walking. The pain is relieved by stopping exercise. The symptom is caused by insufficient blood flow to meet the increased demand of exercising muscles. In the Swedish general population, the prevalence was 7.1% in men and 6.6% in women with a median age of 71 years (Sigvant et al. 2007).

In diabetic patients, neuropathy may abolish the sensation of pain. However, diabetic patientss had a more than two-fold risk of claudication in a US study, in which prevalence of claudication in the general population was 0.9%–1.9% in men and 0.4%–1.1% in women, depending on age (45–84 years) (Murabito et al. 1997). Of diabetic patients, 5.1% had claudication, whereas the proportion of claudicants among non-diabetic patients was 2.1% in another study (Lange et al. 2004).

2.2.1.3 CRITICAL LIMB ISCHAEMIA /CHRONIC LIMB-THREATENING ISCHAEMIA

The term critical limb ischaemia was defined in 1982 to describe lower limb ischaemia that places the limb under the threat of amputation unless a revascularisation is performed (Jamieson 1982). The definitions have later varied (Table 1). Recently, the term chronic limb-threatening ischaemia (CLTI) has been adopted (Conte et al. 2019). A new category of “subcritical” ischaemia was proposed by Wolfe et al. in 1997 and later supported by the European Society for Vascular Surgery (Wolfe et al. 1997, Becker et al. 2011). Limbs threatened with amputation may need different efforts than limbs with delayed healing and non-healing of ulcers (Becker et al. 2011). Indeed, the WIfI classification presents 4 grades for ischaemia (Mills et al. 2014). It is estimated that the incidence of CLTI in the general population is 500–1 000/ 1 million inhabitants per year (Norgren et al. 2007).

Approximately half of the patients with DFU attending specialist clinics have ischaemia. In the Eurodiale study, LEAD was found by means of ABI measurements in 22%–73% of the patients with a diabetic foot ulcer, depending on the centre, and a total of 49% of

these patients had an ABI of < 0.9 and/or non-palpable arteria tibialis posterior (ATP) and arteria dorsalis pedis (ADP) pulses, while 12% had an ABI of < 0.5 (Schaper 2012). In a Swedish study, 49% of the diabetic foot ulcers were neuroischaemic, based on an ankle pressure of < 80mmHg, a toe pressure of < 45 mmHg, or Wagner grades 4 and 5 whenever pressures were not obtained (Gershater et al. 2009). In a surgical series from a Helsinki University Hospital clinic, 50% of the patients undergoing infrainguinal bypass due to an ischaemic tissue lesion had diabetes mellitus (Söderström et al. 2008).

Table 1. Definition of CLI and CLTI (chronic limb-threatening ischaemia)

Jamieson 1982	Lower limb ischaemia that threatens the limb with amputation unless a revascularisation is performed.
Second European Consensus Document on Chronic CLI 1991	Ankle pressure below 50 mmHg or toe pressure below 30 mmHg.
TASC I (Dormandy and Rutherford 2000)	Ankle pressure < 50–70 mmHg or toe pressure < 30–50 mmHg or reduced supine forefoot $TcpO_2$ < 30–50 mmHg.
TASC II (Norgren et al. 2007)	Objectively proven arterial occlusive disease.
IWGDF and ESVS recommendations (Cao et al.2011)	Ulcer healing is severely impaired if ABI <0.6. Values > 0.6 should not be trusted. Nevertheless, toe pressure and $tcpO_2$ < 30mmHg would indicate severely impaired healing whereas toe pressure > 55 mmHg and $tcpO_2$ > 50 mmHg would be favourable regarding healing.
Guidance by IWGDF on diabetic foot ulcer and peripheral arterial disease (Brownrigg et al. 2016)	The presence of ABI 0.9–1.3, toe brachial index ≥ 0.75, and the presence of triphasic pedal Doppler arterial waveforms largely exclude LEAD. Imaging studies and subsequent revascularisation should be considered if toe pressure is < 30 mmHg or $TcPO_2$ < 25 mmHg, and if the ulcer is not healing in 6 weeks.
CLTI (Conte et al. 2019)	Presence of LEAD in combination with rest pain, gangrene, or a lower limb ulceration with > 2 weeks' duration. The role of accurate clinical classification is emphasised. WIfI classification is recommended.

ESVS European Society for Vascular Surgery, TASC Transatlantic Intersociety Consensus, IWGDF International Working Group for Diabetic Foot, LEAD lower extremity arterial disease, CLI (critical limb ischaemia), CLTI (chronic limb-threatening ischaemia)

2.2.1.4 DISTRIBUTION OF LEAD IN DIABETIC PATIENTS

In diabetic patients with foot ulcers or gangrene, atherosclerosis typically occludes and obstructs arteries below the knee and the arteria profunda femoris. The lesions are typically multilevel, often bilateral and are common both in men and women. (Jude et al. 2001, Diehm et al. 2006, Graziani et al. 2007, Apelqvist et al. 2011.) In 413 diabetic

patients undergoing endovascular treatment for CLTI, 7% had a > 50% stenosis only in the popliteal or more proximal arteries and 32% only in the infrapopliteal arteries, while 60% had both infrapopliteal and more proximal stenosis (Faglia et al. 2009). In a cohort of 1,046 diabetic patients with ischaemic foot ulcers, 314 (30%) patients underwent percutaneous transluminal angioplasty (PTA) and 190 (18%) vascular reconstruction. In 46% of the endovascular cases, the crural arteries were treated and 51% of the open-surgical reconstructions had truncal or lower run-off (Apelqvist et al. 2011). A cohort of ischaemic diabetic feet showed occlusion in 25% of the fibular arteries, in 56% of the posterior tibial arteries (ATP)s, in 53% of the anterior tibial arteries (ATA)s, and in 12% of the tibiofibular trunks (Aerden 2014).

2.2.2 EPIDEMIOLOGY IN DIABETES

Great variation in epidemiological data on LEAD in diabetic patients exists regarding the study population and the definition of LEAD (Table 2 and Table 3). Large, population-based register studies mostly rely on diagnosis and symptomatic disease. A recent review estimates that the prevalence of LEAD varies between 10% and 40% in general diabetic populations (Hinchliffe et al. 2016).

In a register study consisting of the entire type 2 diabetic population over 35 years of age in the Basque Country, the prevalence of peripheral arterial disease was 2.5%. It was more prevalent in men (3.95%) than in women (0.97%). (Alonso-Morán et al. 2014.) In a population-based survey from Wales, 9% of diabetic patientss (mean age 60–61 years) had a diagnosis of diabetic foot or peripheral vascular disease. Notably, 16% of diabetic men over 50 years of age had LEAD based on their medical records, but when all patients with an ABI of < 0.9 were included, the prevalence was 30% (Hirsch et al. 2001). In an Australian population-based study of persons over 25 years of age, 13.6% of individuals with known diabetes and 6.9% of newly diagnosed diabetics had LEAD, as defined with ABI and a claudication questionnaire. The prevalence increased with the duration of diabetes, reaching 31.3% after 20 years' duration. (Tapp et al. 2003.) In a Scottish population-based study, 17% of all diabetic patients (mean age 59 years) had absent foot pulses (Leese at al. 2011).

In an English population-based cohort of 1.9 million individuals, including 34,198 diabetic patients aged over 30 years with no previous cardiovascular events, 992 (2.9%) of the diabetic patients experienced the first presentation of LEAD during a mean 5.5-year follow-up time, constituting 610/100 000 person years (Shah et al. 2015)

Table 2. Prevalence of LEAD in diabetic patients.

Study	patients	prevalence	method	else
Charles et al. 2011	1 533 screened DM patients from GP	7.3%-9.1%/ 6-year-fup	ABI	intensive/ routine treatment groups NS difference, mean age 60 yrs
Lange et al. 2004	6 880 all/1743 DM consecutive GP multicentre	26.3% DM/ 15.3% nonDM	ABI < 0.9	≥ 65y, mean 72.5 yrs, ABI, physical examination, interview
Lange et al. 2004	6 880/1743 DM consecutive GP multicentre	5.1%DM/2.1 % nonDM	claudication	≥ 65 y, mean 72.5 yrs, ABI, physical examination, interview
Shah et al. 2015	3.7 million cohort, 400 000 any diabetes	11.5%	ABI, patient-reported history of arterial intervention or claudication	Lifeline screening survey, not (but near) population-based, mean age 66.5 years
Alonso-Moran et al. 2014	149 000 type 2 DM subjects	2.5%	register-based diagnosis	over 35-yr-old population of the Basque Country
Jensen et al. 2006	20 300 local population Norway, 500 DM	1.2% DM/ 0.2% non-DM	questionnaire on CLTI symptoms	population-based, 40–69 years
Baser et al. 2013	98% US population > 65 years	0.19% DM/ 0.04% non - DM	CLTI and rest pain, inpatient and outpatient dg	any diabetes
Baser et al. 2013	98% US population > 65 years	0.84% DM/ 0.08% non-DM	CLTI and ulcer or gangrene inpatient and outpatient dg	any diabetes
Morgan et al. 2010	439 000 local population, Wales DM 17 100	9%	diabetic foot and LEAD	register-based diagnosis
Tapp et al. 2003	11 247 random cohort of Australian population, 853 DM2	14% known DM, 7% new DM	ABI, claudication	≥ 25 years, mean LEAD 72 years, no LEAD 62 years
Leese et al. 2011	Scottish diabetes register 3 719 patients	17.2%	pulse palpation, both pulses absent	population-based

GP general practitioner, DM diabetes mellitus, LEAD lower extremity arterial disease, CLTI chronic limb threatening ischaemia, US United States.

Table 3. Incidence of LEAD in diabetic patients

Study	patients	incidence	method	characteristics
Baser et al. 2013	98% US population > 65 years	0.17%	CLTI and rest pain inpatient and outpatient dg	any diabetes
Baser et al. 2013	98% US population > 65 years	0.69%	CLTI and ulcer or gangrene, inpatient and outpatient dg	any diabetes
Shah et al. 2015	1.9 million UK population-based cohort	610/ 100 000 person years	LEAD, register-based diagnosis, primary care, hospital discharge, death registration, myocardial ischaemia register	> 30 years, no previous cardiovascular disease

US United States, CLTI chronic limb-threatening ischaemia, LEAD lower extremity arterial disease, UK United Kingdom.

2.2.3 DM AS A RISK FACTOR FOR LEAD AND THE PROGRESSION OF THE DISEASE

Diabetes is a strong risk factor for asymptomatic and symptomatic LEAD and its progression. The prevalence of LEAD is estimated to be from 3 to 4 times higher in the diabetic than the non-diabetic population (Norgren et al. 2007). In a meta-analysis including community-based studies in high-income countries from 1997 onwards, diabetes was a risk factor (OR 1.88) for LEAD, as defined by an ABI ≤ 0.9, in people over 25 year of age. The other risk factors included in the study were smoking, hypertension and hyperlipidaemia. (Fowkes et al. 2013.)

Diabetes predicts the progression of LEAD. A meta-analysis showed a progression from claudication to CLTI during five-year follow- up in 21% of the patients. Diabetes (OR 2.33), stroke (OR 1.22) and heart failure (OR 1.36) increase the risk of LEAD progressing to CLTI. (Sigvant et al. 2016.) However, claudication does not necessarily precede critical limb ischaemia. This is typical in patients with diabetes, heart failure, renal failure and stroke. In an extensive register-based study in the US, 11% of the general population with claudication developed CLTI annually. The risk of CLTI without prior LEAD was high in diabetes (OR 7.45). (Nehler et al. 2014.)

A French population-based study showed that patients who became diabetic developed LEAD (ABI and claudication questionnaire) twice as often as patients who remained normoglycaemic (Tapp et al. 2007). In an American study with over 3 million

participants, diabetic patients had an increased risk of LEAD when compared to non-diabetic individuals, with an odds ratio of 1.96. When adjusted for age, sex, ethnicity, hypertension, hyperlipidaemia, smoking status, BMI (body mass index), coronary artery disease and transient ischaemic attack (TIA or stroke), the odds ratio was 1.42. The odds ratio for mild LEAD (based on ABI measurements) was 1.37, for moderate LEAD 1.77, and for severe LEAD 2.16 after adjustment. (Shah et al. 2015)
In a study based on US Medicare Data, the annual incidence and prevalence of CLTI was roughly nine times higher in diabetic compared to non-diabetic patients. In diabetic and non-diabetic patients, the prevalence of CLTI and rest pain was 0.19% and 0.04%, respectively, whereas the prevalence of CLTI and tissue lesions was 0.84% and 0.08%, respectively. In patients with CLTI, the incidence of amputation was 31% among diabetic and 17% among non-diabetic patients. The incidence of revascularisation was 29% among diabetic and 31% among non-diabetic patients with CLTI during the first year. (Baser et al. 2013.) The OXVASC study from the UK reports vascular events prospectively in a population of roughly 92 000 subjects during a ten-year period in 2002–2012. An incident CLTI event (rest pain or ulcer for more than 2 weeks needing hospital admission) during the 10-year follow-up was observed in 89/3,125 (2.8%) among diabetics, compared to the 112/89,603 (0.1%) among non-diabetics (RR 5.96 3.15–11.26, p <0.001) (Howard 2015).

2.2.4 ANGIOSOMES

An angiosome is an anatomical three-dimensional area vascularised by one source artery. Three main arteries supply the foot and the leg: the arteria tibialis anterior (ATA), the arteria tibialis posterior (ATP) and the fibular artery. They give altogeather six source arteries which feed the six angiosomes of the foot. The ATA extends to periphery via the ADP and supplies the anterolateral leg, the anterior ankle and the dorsal foot and the toes. The ATP has three main branches: the medial calcaneal branch supplies the medial and plantar heel, the lateral plantar artery the lateral plantar area and the toes and the medial plantar artery the medial plantar surface and the first toe. The fibular artery divides into two main branches: the lateral calcaneal branch supplies the plantar and lateral heel and the lateral ankle and the anterior perforating branch the anterior ankle. The angiosomes overlap especially in the toes and in the heel. (Figure 2), (Attinger et al. 2006, Taylor and Palmer 1987). Remarkably, anatomical variations in arterial tree are common. Furthermore, collaterals and the pedal arch make the system more complex. Revascularisation has been classified as direct, direct through collaterals and indirect. However, agreement on the criteria for these groups is lacking. In one study, the pedal arch was complete in 31 and occluded in 32 out of 167 feet undergoing bypass surgery (Rashid et al. 2013)In another study, in 33% of 106 limbs had an open pedal arch (Kret et al. 2014).

In a study conducted in Helsinki, ulcers were limited to one angiosome in only 24% of the lower extremities, while 47% of the ulcers involved two, 26% three and 3% four or

five angiosomes (Spillerova 2016). The feasibility of angiosome-targeted endovascular revascularisation was considered to increase when the ulcer affected more than one angiosome (Spillerova et al. 2016). In another study, 31% of the ulcers were clearly limited to a single angiosome, 56% were located within two angiosomes, and 7.5 % involved three angiosomes (Kret et al. 2014).

In a further study (Aerden et al. 2014), the location of 345 ulcers in 185 diabetic feet was studied in relation to the angiosomes. Forty-six percent had toe ulcers only, 18% had both toe and more proximal ulcers, and 36% had only proximal ulcers. In 77% of the ulcers, the location in relation to the angiosomes remained ambiguous. Toe ulcers, lateral foot ulcers and heel ulcers were located at the junction of two angiosomes. In some patients, the more proximal ulcer made the selection between the ATA and ATP more obvious. According to Aerden et al., at least 8.6% of patients with diabetic foot ulcers would need revascularisation of two vessels if all ulcer angiosomes in the foot and lower leg were to be revascularised. (Aerden et al. 2014.)

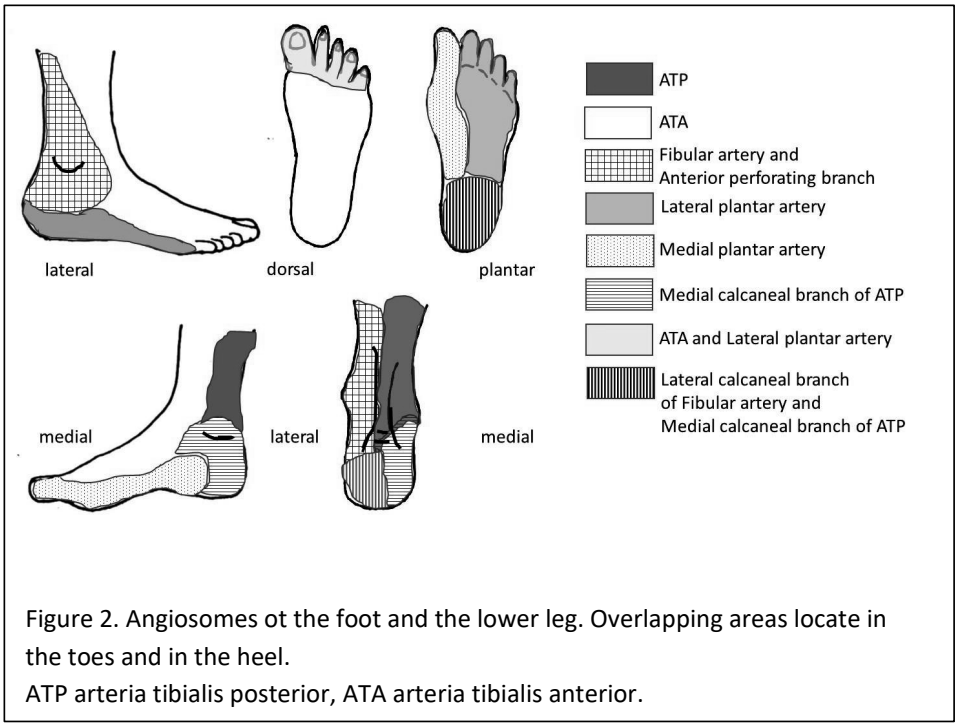

Figure 2. Angiosomes ot the foot and the lower leg. Overlapping areas locate in the toes and in the heel.
ATP arteria tibialis posterior, ATA arteria tibialis anterior.

2.2.5 CLASSIFICATION

The most common clinical classifications of ischaemia are the Fontaine and the Rutherford classification. The Fontaine classification of LEAD was presented in 1952 (Becker et al. 2011) (Table 4). The Rutherford classification of LEAD was created in 1986 and revised 1997 (Rutherford et al. 1997) (Table 5). It first included ankle pressure, toe pressure and pulse volume recording (PVR) criteria in addition to clinical criteria, but these have been later abandoned (Becker et al. 2011). The WIfI classification grades ischaemia based on ABI values and is recommended to be used in all diabetic patients with a foot ulcer (Mills et al. 2014). It is presented among the ulcer classifications later in this dissertation.

Table 4. Fontaine classification.

Grade	Description
1	asymptomatic
2	intermittent claudication
3	ischaemic rest pain
4	ulcer or gangrene

Table 5. Rutherford classification (Reproduced with permission from Rutherford et al. 1997).

0	Asymptomatic	Normal treadmill/stress test
1	Mild claudication	Completes treadmill exercise, ankle pressure after exercise < 50 mmHg but > 25 mmHg lower than blood pressure
2	Moderate claudication	Between classes 1 and 3
3	Severe claudication	Cannot complete treadmill exercise and ankle pressure after exercise < 50 mmHg
4	Ischaemic rest pain	Resting ankle pressure < 40 mmHg, flat or barely pulsatile ankle, or metatarsal PVR; toe pressure < 30 mmHg
5	Small tissue defect	Resting ankle pressure < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; toe pressure < 40 mm Hg
6	Large tissue defect reaching proximal to tarso-metatarsal joints, functionality of the foot not salvageable	Same as 5

2.2.5.1 Glass

The Global Limb Anatomic Staging System (GLASS) classification considers multilevel disease and combines the femoropopliteal and infrapopliteal distribution of disease into three stages based on the estimated immediate technical failure rate and the leg-based patency at one year. In femoro-popliteal and infrapopliteal segments, the length of the diseased and occluded arterial segments and the severity of stenosis are graded. The inflow and inframalleolar disease are evaluated separately. (Conte et al 2019.)

2.2.6 DIAGNOSIS OF LEAD IN DIABETIC PATIENTS

2.2.6.1 NONINVASIVE METHODS

Simple and reliable bedside diagnostic methods for LEAD among diabetic patients are still required. Approximately 50% of diabetic ulcers are of ischeamic aetiology. Therefore, it is not effective to screen ischaemia with very ponderous protocols. Pulse palpation is a clinical basic examination of every patient, but the repeatability and reliability of pulse palpation have been questioned (Brownrigg et al. 2016). Up to 20% of arterial disease confirmed by colour duplex imaging were missed with pulse palpation (Williams et al. 2006). While the palpation of pulses in screening for LEAD is not an optimal method, it does predict the ulcer risk. A meta-analysis of individual patient data of 16 000 subjects worldwide showed that monofilament testing and pulse palpation are effective methods for screening diabetic feet at risk of ulceration (Crawford et al. 2015). Furthermore, in a Scottish population-based study, absent foot pulses and neuropathy assessed by means of monofilament testing, among other factors, predicted ulceration in diabetic patients with no previous ulcers. Absent pulses also predicted amputation as well (Leese et al. 2011).

ABI is the basic method to diagnose lower extremity arterial disease, and values < 0.9 have good sensitivity and specificity to detect LEAD in the general population. Ankle pressure or ABI never exclude significant LEAD in diabetic patients. Medial sclerosis makes the artery walls stiff and poorly compressible in 30%–50% of diabetes with foot lesions (Lepäntalo et al. 2011, Faglia et al. 2010, Acin et al. 2014, Prompers et al. 2007). Thus, circulation may be poor when the ABI is 1.0–1.4 (Conte et al. 2019).

In the Eurodiale study, the ABI was over 1.2 in 32% of the patients (Prompers et al. 2007). Toe pressure measurement and tcOp2 have been suggested as alternative noninvasive methods to detect LEAD in diabetic patients. Medial sclerosis is rare in the digital arteries (Williams et al. 2006). Nevertheless, necrosis or a previous amputation of toes prevents the measurement of toe pressure in many patients – in an Italian material, in 16% of the patients (Faglia et al. 2009). User-friendly equipment is available, but the quality control and interpretation of the results require some expertise. Furthermore, the repeatability

of toe pressure measurements with the most affordable devices is compromised (Widmer et al. 2013). $TcpO_2$ measurement is useful in capable hands. In an Italian specialist clinic, $tcpO_2$ was measurable in all 261 diabetic patients, whereas ankle pressure could be measured in 58% and toe pressure in 72% of the patients. All patients had > 50% stenosis in angiography (Faglia et al. 2010). However, the examination is time-consuming and requires equipment and expertise, making it non-optimal for screening purposes. Lower $tcpO_2$ values have been shown in diabetic than in non-diabetic patients with arterial disease and with similar TBIs, which is most pronounced in the presence of neuropathy. Diabetic patients are suggested to have worse perfusion than non-diabetic patients in the presence of similar macrovascular disease pattern (Williams et al. 2006).

Triphasic flow in qualitative visual Doppler waveform analysis has been suggested for screening of LEAD in diabetic and nondiabetic patients (Brownrigg et al. 2016). A study on the ability of the loss of reverse flow to indicate obstructions in the arterial tree showed that the false negative rate regarding triphasic flow was quite low: 15% in non-diabetic and 6% in diabetic atherosclerotic patients (Williams et al. 2005).

2.2.6.2 IMAGING

Digital subtraction angiography (DSA) is the gold standard in diagnosing significant arterial disease. Recently, however, DSA has been used mostly for endovascular procedures, whereas magnetic resonance angiography (MRA), computed tomography angiography (CTA) as well as ultrasound have replaced it as a first line diagnostic method (Conte et al 2019). Nevertheless, DSA generally results in the best-quality images of crural and pedal outflow arteries. Furthermore, in patients with severe nephropathy or a cardiac pacemaker, angiography may serve as a part of the diagnostics. Angiography has many disadvantages, including its invasiveness, the nephrotoxity of contrast media and radiation (van der Molen et al. 2018). Nefrotoxity can be avoided with CO_2 as contrast medium, and images of reasonable quality can be achieved (Palena et al. 2016). In a Swedish study, 99 complications ensued in 72/801 (9%) patients after angiography. The most frequent were renal impairment, with in 56 cases, and haemorrhage, which occurred in 26 cases. One patient had an occlusion, and the rest were miscellaneous complications (Apelqvist et al. 2011). In practice, several imaging modalities may be necessary (Conte et al. 2019).

2.3 DIABETIC FOOT ULCERS

Diabetic foot problems are one of the most common and most expensive complications of diabetes. As regards the costs of diabetes, 20%–40% are due to diabetic feet (Lepäntalo et al 2011). The problems initiate with skin/tissue lesions that progress into chronic ulcers and can lead to minor and major amputations. Of major amputations, 80%–90% are preceded by an ulcer (Lepäntalo et al. 2011). In a multicentre study comprising data on a cohort of 1,229 patients from 14 European multidisciplinary clinics, the ulcers in diabetic patients with LEAD had more extensive tissue loss, reached the bone or joint more often and were larger than the ulcers in patients without LEAD (Schaper 2012).

2.3.1 EPIDEMIOLOGY

The estimation of the lifetime risk of ulceration in diabetic patients is 15%–25% (Singh et al. 2005, Schaper 2012). Incidence and prevalence numbers vary in relation to the population under study and the reference population. Furthermore, the method of data collection affects the numbers (Forssgren and Nelzen 2015, Hopkins et al 2015). Typically, cohorts retrieved from specialist clinics or hospitals have a higher incidence and prevalence and they are not representative regarding population based epidemiological data.

The point prevalence of diabetic foot ulcers in different studies varies between 1.5% and 10% of diabetic patients(Singh et al. 2005, Forssgren and Nelzen 2012). In a register study consisting of the whole type 2 diabetic population of the Basque Country, the prevalence of foot ulcers was 1.93% in 2011 (Alonso-Morán et al. 2014). The point prevalence of DFU in 2011 was 0.13 per a general population of 1,000 in Leeds, UK (Hall et al. 2014).

In Sweden, an epidemiologic study of foot and leg ulcers was repeated in the same geographical area with 250 000 inhabitants in 1988 and 2002. In 1988, 3.5% of diabetic patients had a foot or leg ulcer, compared to 2.2% in 2002. Of all patients with foot ulcers, 32% had both ischaemia and DM, and 24% of the ulcers were non-ischaemic diabetic ulcers. (Forssgren and Nelzen 2012.) In another study, a questionnaire was sent to a randomly selected sample of inhabitants in the same area in 2005. Ulcers were verified by clinical examination. The prevalence expected based on the preceding questionnaire sent to professionals was 0.23, whereas the prevalence obtained with the questionnaire to the inhabitants was 0.52 (Forssgren and Nelzen 2015).

The mean annual incidence of new and recurrent ulcers was 6.1 and 7.1/1,000 diabetic patients, respectively, in a NHS (National Health Service) area in the UK during 2013-2017 (Paisey et al. 2019). In Scotland, 1.93% of consecutive ambulant diabetic patients over 18 years of age with intact skin visiting a community-based primary care podiatric

clinic developed an ulceration during 1-year follow-up (Crawford et al. 2011). Based on register data in Canada, the incidence of diabetic foot ulcers in 2011 was 42.4/a general population of 100 000. A 7.4% yearly increase in the incidence of diabetic foot ulcers was observed over the 5 preceding years (Hopkins et al. 2015). In a Japanese special diabetic clinic, the foot ulcer incidence was 2.9/1,000 patient years (Iwase et al. 2018).

In a Danish specialist diabetes centre, the incidence of foot ulcers among type 1 diabetic patients was 8.1/1,000 patient years in 2002 and 2.6/1,000 patient years in 2014. The study population was representative of the Danish type 1 diabetic population. During 2002–2014, the incidence of neuropathic ulcers was 2.57/1,000 patient years, of neuroischaemic ulcers 2.19/1,000 patient years and of critically ischaemic ulcers 0.47/1,000 patient years. Of the type 1 diabetic patients included in the cohort, 47% were under 40 years of age. (Rasmussen et al. 2017.) In a Swedish cohort study, 18% of the patients with diabetic foot ulcers had type 1 diabetes (Gershater et al. 2009).

In an Australian population-based study of persons over 25 years of age, 2.1% of diabetics reported a previous foot ulceration; 3% of patients with known diabetes and 1.2% of patients with newly diagnosed diabetes (Tapp et al. 2003). A hospital-discharge-register-based survey from 1996–2000 covering the US showed that diabetic patients over 80 years of age had more foot complications than non-diabetic patients. Foot ulcers were present in 1.7% of the diabetic and 0.6% of the nondiabetic patients(Reed 2004). The main aetiologic factor was diabetes without LEAD in 132 000 patients, LEAD without diabetes in 36 000 patients and both LEAD and diabetes on in 52 000 patients in a Californian register-based study of patients with a total of 220 000 incident ischaemic or diabetic lower extremity ulcers during 2005–2013 (Humphries et al. 2016).

2.3.2 AETIOLOGY

Ischaemia and neuropathy are the most important aetiological factors of diabetic foot ulcers. Decreased resistance to infections, , is rather one of factors predicting the outcome of diabetic ulcers. (Lepäntalo et al. 2011)Traditionally, ulcers have been categorised into aetiological subgroups, but in clinical practice, multiaetiological ulcers are common. Forty-three percent of the below-knee ulcers in a population-based study were multiaetiolgical based on a clinical examination (Forssgren and Nelzen 2012). A diabetic patients probability of developing an ulcer on intact skin can be predicted by three variables: reduced sensation in monofilament testing, the absence of at least one pedal pulse and a previous history of an ulcer or an amputation (Crawford et al. 2015). In specialised diabetic foot clinics in Europe, approximately half of the ulcers are neuroischaemic and another half neuropathic. Ischaemia was defined according to ABI and toe pressure values and/or absent pulses (Prompers et al. 2007, Gershater et al. 2009). The absence of both ischaemia and neuropathy is rare in diabetic foot ulcers. In Scotland, 70% of 221 consecutive patients visiting a regional specialist foot clinic had

absent foot pulses and 82% an absence of sensation in monofilament testing. Only 2% of the ulcers that were referred to a specialist foot clinic were in low-risk feet with pulses and no neuropathy (Leese et al. 2007). Among 194 patients with diabetic foot ulcers evaluated at a specialist clinic, 11 (5.6%) had neither ischaemia nor moderate to severe neuropathy (Oyibo et al. 2001). In an English diabetic foot centre, 80% of the patients with an ulcer had neuropathy (Jeffcoate et al. 2006).

Typically, multiple factors influence the causal pathway leading to a non-healing ulcer (Reiber 1999). Several different factors, such as foot deformities, external pressure or trauma, can initiate ulcers, as can some diseases. Often the cause of an ulcer remains unknown. Table 6 is summarises factors causing an ulcer.

The most common pathway to ulceration has been reported to be the combination of neuropathy, minor trauma and foot deformity, which was present in > 63% of the ulcers in a study conducted at diabetic foot clinics in Seattle and Manchester. Out of the individual factors, oedema, ischaemia and callus formation were present in 37%, 35% and 30% of the pathways, respectively. Notably, the frequency of single factors at the two centres was different (Reiber et al. 1999).

Table 6. Examples of factors initiating ulceration

Causative factors for DFU	specific conditions/incidents causing ulcers
foot deformation	hammer toes, mallet toes, claw toes, prominent metatarsal heads charcot, hallux valgus, callosities
other foot problems	paronychia, skin cracks
external pressure	footwear, compression stockings and bandages, plaster cast, madrass, bed rails and ends
trauma	abrasion, blisters, insect bites, fractures, luxations, crush injuries, wounds, foreign bodies, haematoma, burn, cold, chemicals, lacerations, fractures.
iatrogenic trauma	surgical wound, amputation wound, revision wound, corrective surgery, arthroplasties, biopsies, foot care, self-induced ulcers
diseases	erysipelas, fascitis, gout, eczema, malignancy, rare ulcerative infections

2.3.3 CLASSIFICATION

Several classification methods have been introduced to describe diabetic foot ulcers. Many aspects should be considered regarding an ulcer scoring system, such as the field of use, i.e. clinical or research, and the characteristics of the patient cohort. Few ulcer classifications have been validated or their inter-observer variation assessed (Karthikesalingam et al. 2016). The most common classifications are the Meggit-Wagner (MW), University of Texas (UT), and WIfI classifications.

Table 7. Meggit-Wagner classification. Reproduced with permission from Wagner 1981.

0	Pre- or post-ulcerative lesion, completely epithelialised
1	Superficial full-thickness ulcer limited to the dermis, not extending to the subcutis
2	Ulcer of skin extending through the subcutis with exposed tendon or bone
3	Deep ulcer with abscess or osteomyelitis
4	Localised gangrene of the toes or the forefoot
5	Foot with extensive gangrene

Table 8. The University of Texas wound classification system. Reproduced with permission from Armstrong et al. 1998.

Stage	Grade 0	Grade 1	Grade 2	Grade 3
A No infection or ischaemia	Pre- or post-ulcerative lesion, completely epithelialised	Superficial ulcer, not involving tendon, capsule or bone	Wound penetrating to ulcer or tendon or capsule	Wound penetrating to bone or joint
B Infection	Pre- or post-ulcerative lesion, completely epithelialised with infection	Superficial ulcer, not involving tendon, capsule or bone with infection	Wound penetrating to ulcer or tendon or capsule, with infection	Wound penetrating to bone or joint with infection
C Ischaemia	Pre- or post-ulcerative lesion, completely epithelialised with ischaemia	Superficial ulcer, not involving tendon, capsule or bone with ischaemia	Wound penetrating to ulcer or tendon or capsule, with ischaemia	Wound penetrating to bone or joint with ischaemia
D Infection and ischaemia	Pre- or post-ulcerative lesion, completely epithelialised with infection and ischaemia	Superficial ulcer, not involving tendon, capsule or bone with infection and ischaemia	Wound penetrating to ulcer or tendon or capsule, with infection and ischaemia	Wound penetrating to bone or joint with infection and ischaemia

The MW classification was generally used clinically and in research before the University of Texas (UT) classification sgained popularity (Wagner 1981) (Table 7). It has not been validated, and the description of an ulcer is quite poor in its nuances.

The UT classification systematically combines ulcer depth with infection and ischaemia (Lavery et al. 1997) (Table 8). Increasing grade and stage were associated with midfoot

and more proximal lower leg amputations. (Armstrong et al. 1998). The UT and MW classifications were compared in a cohort of 197 small ulcers dominated by neuropathy. Sixty-seven percent of the ulcers were neuropathic and 26% neuroischaemic. The association with lower extremity amputation and ulcer healing was assessed. Lower extremity amputation was not defined, but as the amputation rate was 15%, it can be concluded that all amputations including toe amputations are probably included. Increasing grade in the MW and UT classifications was associated with lower extremity amputation, whereas the UT classification stage was also associated with ulcer healing (Oyibo et al. 2001).

As a development to earlier classifications, the WIfI classification quantifies infection and ischaemia, in addition to defining the depth of the ulcer and its location in the heel. The "W" refers to wound, "I" to ischaemia and the final "fI" to foot infection. Different combinations of grades were assessed by experts, and each was evaluated into the stages of very low, low, moderate or high risk of amputation (Mills et al. 2014) (Table 9a-d). A review based on 12 retrospective studies published before the era of the WIfI classification concludes that the risk of amputation increases with the higher WIfI stages (Van Reijen et al. 2019). The identification of patients who would probably benefit from revascularisation was studied with clusters of WIfI combinations formed based on the difference in predicted and observed lower extremity amputation rates among patients who underwent revascularisation. After revascularisation, the wound characteristics were associated with lower extremity amputation (Mayor et al. 2019).

Table 9a. Wound grades in the WIfI classification. Reproduced with permission from Mills et al. 2014.

Grade	Ulcer	Gangrene
0	No ulcer	No gangrene
1	Small, shallow ulcer(s) on distal leg or foot No exposed bone, unless limited to distal phalanx	No gangrene
2	Deeper ulcer with exposed bone, joint or tendon Shallow heel ulcer, without calcaneal involvement	Gangrene in toes
3	Extensive, deep ulcer involving forefoot and/or midfoot Deep, full thickness heel ulcer 6 calcaneal involvement	Extensive gangrene involving forefoot and/or midfoot Full-thickness heel necrosis ± calcaneal involvement

Table 9b. Ischaemia grades in WIfI classification.

Grade	ABI	ankle mmHg	toe pressure mmHg
0	> 0.8	> 100	> 60
1	0.6–0.79	70–100	40–59
2	0.4–0.59	50–70	30–39
3	< 0.39	< 50	< 30

Table 9c. Infection grades in the WIfI classification. Reproduced with permission from Mills et al. 2014 and Lipsky et al. 2012.

Clinical manifestation of infection	Grade	IDSA/Pedis infection severity
No symptoms or signs of infection	0	no infection
Local infection (No systemic signs) involving only the skin and the subcutaneous tissue, at least 2 of the following: Local swelling or induration, Erythema > 0.5 to 2 cm around the ulcer, Local tenderness or pain, Local warmth, Purulent discharge, Exclude other causes of an inflammatory response (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)	1	mild
Local infection (No systemic signs) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis)	2	moderate
Local infection with the signs of SIRS, as manifested by two or more of the following: Temperature > 38 > 90 beats/min Respiratory rate > 20 breaths/min Elevated infection markers	3	severe

SIRS systemic inflammatory response syndrome.

Table 9d. WIfI classification clinical stages based on expert consensus.

	ischaemia 0				ischaemia 1				ischaemia 2				ischaemia 3			
W0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3

2.3.3.1 LOCATION

Common classification of ulcer location is lacking. Foot ulcers but also ulcers in the ankle and leg are often included in publications. Often the term 'leg ulcer' comprises ulcers in the foot as well. Generally, leg is the most common location of chronic lower extremity ulcers. In Swedish population-based study 70% of all ulcers located above the ankle, and this proportion was 10-14% in diabetic patients (Forssgren and Nelzen 2012). However, in diabetic patients the most frequent location is toes, independent of the setting. (Prompers 2007, Apelqvist 2011) In Eurodiale study 55% of the ulcers were in the toes, 32% dorsally or interdigitally and 48% were plantar. 23% of the ulcers were on the plantar forefoot, 22%in plantar midfoot, and 3% on the plantar hind foot, 10% in the heel, and 10% on the dorsal or lateral aspect of the foot. 40.9% of the ischaemic and 55% of the non-ischemic ulcers were plantar. (Prompers et al. 2007, Prompers et al. 2008) Frequently more than one ulcer is found. In a cohort from diabetic foot clinic, a half of 185 feet had more than one ulcer (Aerden et al. 2014)

2.3.3.2 DEPTH OF THE TISSUE LESION

The classification of depth is typically reported based on the Texas or Wagner classifications, but population-based data on ulcer depth is non-existent. In studies from specialist foot clinics and surgical series, 15%–55% of the patients have an ulcer extending beyond the subcutis.

In the Eurodiale study, 53% of the ischaemic ulcers and 36% of the non-ischaemic ulcers extended beyond the subcutis and were classified as deep. Sixty-four percent of the UT stage D ulcers were deep, whereas 20% of stage A ulcers were deep. (Prompers et al. 2007, Prompers et al. 2008) In a series from a multidisciplinary clinic, 10% of the ulcers were MWgrade 3 and 6% grades 4–5, including both purely neuropathic and neuroischaemic ulcers (Gershater et al. 2009). In Scotland, 44% of the ulcers of 221 consecutive patients visiting a regional specialist foot clinic were superficial, 18% were deep and 38% reached bone (Leese et al. 2007). In Helsinki, among 113 patients who underwent infrainguinal bypasses for CLTI and foot ulcers, 41% had UT 1C lesions, 19% had 1D lesions, 10% had 2C, 2D and 3C lesions each, and 23% had 3D lesions. Fifty percent of the patients were diabetics (Söderström et al. 2009).

The depth in the same material varies at different points in time, as shown by a Swedish study: of 475 diabetic patients with a foot ulcer and LEAD, 21% had a Wagner grade 3 or higher at inclusion. During the study, a total of 55% reached Wagner grade 3 or higher at some stage (Elgzyri et al. 2014).

2.3.4 ULCERS AND INFECTION

Infection is defined in IWGDF as invasion and multiplication of microorganisms in host tissues that induces a host inflammatory response, usually followed by tissue destruction. Diabetic patients have decreased resistance to infections, which correlates with glucose balance. A known deficit is the impairment of the bactericidal activity of polymorphonuclear cells. Furthermore, the clinical signs of infection may be attenuated.

Neuropathy may aggravate infection by hiding the signs of infection and by altering the microcirculation. Autonomic neuropathy in the form of C-fibre dysfunction may diminish the inflammatory reaction. Absent local nerve stimulus results in a deficient release of inflammatory cytokines. The opening of arteriovenous shunts leads to an increase in intravenous and tissue pressure and deep tissue ischaemia. The loss of protective sensation leads to the aggravation of the infection before it is noticed. (Richard et al. 2012.)
Bacterial biofilms seem to act in most chronic diabetic foot ulcers (James et al. 2008). Biofilms may prevent antibiotics from reaching the bacteria. The resistance to antibiotics may increase as great numbers of bacteria exchange information during the colonisation. In the polymicrobial circumstances of biofilms, one antibiotic is not necessarily effective against all pathogens (Mottola et al. 2016).

In clinical practice, a diagnosis is based on a clinical decision, basic laboratory tests, radiologic imaging, and close follow-up. For research purposes, the definition of infection remains equivocal (Lipsky et al. 2019).
The identification of a severe limb-threatening infection needing surgical revision may be difficult (Clerici and Faglia 2014, Lipsky et al. 2019). The clinical signs are numerous but not specific to infection. In diabetic patients, they are frequently absent or diminished (Lipsky et al. 2019). Furthermore, in ischaemic ulcers before and after revascularisation, redness, swelling and pain are often present. Patients with a deep foot infection may have undiagnosed diabetes in the background.

2.3.4.1 EPIDEMIOLOGY OF DIABETIC FOOT INFECTIONS

Recent epidemiological data on diabetic foot infections is scarce. However, the incidence of infections seems to be decreasing, at least in the US. In a US discharge register, 1 059 552 diabetic foot infections were identified between 1996 and 2010. The total number of diabetic foot infections decreased by 11% and the incidence per 100 diabetic admissions by 52% within this period. (Duhon et al.2015.)

In another American study of 1,666 consecutive diabetics enrolled in a diabetic foot prevention and treatment programme in the US, 9% developed a foot infection during the mean 27 month follow-up (Lavery et al. 2007). In the Eurodiale study, 591 (58%) of the 1,033 patients who completed the study had an infection when seen at a foot clinic in 2003–2004. Of the 575 patients with complete data, 199 (35%) patients had a grade 2 (mild) , 338 (59%) a grade 3 (moderate), and 38 (7%) a grade 4 (severe) infection (Prompers et al. 2007, Pickwell et al. 2015).

Remarkably, diabetic foot infections are usually preceded by a foot ulcer. In the aforementioned American cohort of 1,666 diabetics, there was only one case among the 199 foot infections that appeared in which no foot ulcer was present. At enrolment, 247 patients had an ulcer, and 61% of the patients developed an infection (Lavery et al. 2006). Most frequently, the infection originates in the forefoot. In a French study, 45% of the infected ulcers were in the toes and 34% in the forefoot. Protective sensation, as assessed in 278 patients by the 10-g monofilament test, was lost in 252 patients (87%), and Charcot foot deformity was present in 39 (13%) (Richard et al. 2011).

Concomitant ischaemia and infection are common in feet with DFU. Accordingly, 65% of the patients operated on because of an acute infection and osteomyelitis had LEAD based on pulse palpation, ABI and $tcpO_2$ (Aragon-Sanchez et al. 2008). In a French Opidia study 50-62% of diabetic patients clinical examination revealed LEAD (Richard et al 2011).On the contrary, of the patients with a diabetic foot infection,16.4% had a diagnosis of LEAD in a large material from an American discharge register (Duhon et al. 2015). Probably register based data ignored comorbidities. The risk of infection has been reported to be 2- to 5.5-fold in patients with LEAD compared to those with no LEAD (Peters et al. 2015, Lavery et al. 2006, Duhon et al. 2015).

2.3.4.2 OSTEOMYELITIS

Osteomyelitis is present in roughly 50%–60% of acute infections requiring in-hospital treatment and in approximately 10%–20 % of more chronic infections treated in an outpatient setting (Lavery et al. 2007, Richard et al. 2011).

Osteomyelitis is an infection of the bone, which leads to structural changes and lysis of the bone, but regeneration of the bone also occurs. Interestingly, even total regeneration of bone that is revealed to be widely lysed in x-ray imaging during antibiotic treatment is possible (Jeppesen et al 2015). Osteomyelitis can perform as an acute or as a chronic infection.

The diagnosis of osteomyelitis is based on the probe-to-bone test, serum infection markers (e.g. CRP, procalcitonin, ESR) and plain x-ray imaging. In chronic osteomyelitis, leukocyte counts are not necessarily elevated, but CRP and the sediment elevation rate are more sensitive. In ambiguous cases, advanced imaging, such as MRI, PET-CT or scintigraphy, is recommended. If necessary, to confirm the diagnosis and to direct the antibiotic regimen, bone biopsy as well as a microbiological culture and histological examinations are useful. The typical culprit bacteria are the same as in soft tissue infections and other types of chronic ulcers, the most frequent being staphylococcus aureus and beta-haemolytic streptococci. (Lipsky et al.2019.)

2.3.4.3 TREATMENT OF INFECTION

DNA analysis of the bacterial composition of 2,936 chronic wounds revealed that the general pathogens in diabetic foot infections are the same as in other chronic ulcers. The most abundant bacterial species was staphylococci, followed by pseudomonas, corynebacteria and streptococci (Wolcott et al. 2015).

The IWGDF guidelines advocate covering gram-positive cocci such as staphylococcus aureus and beta haemolytic streptococcus. The treatment of common gram-negative bacteria and possibly obligate anaerobes is suggested in chronic ulcers with a moderate or severe infection, with severe ischaemia or a history of treatment with antibiotics (Lipsky et al. 2019). Worldwide, multiresistant bacteria have become more common. However, when appropriately treated, the clinical infection seems not to differ from other bacteria (Uckay et al. 2015).

Revision surgery is often mandatory in an acute infection because of soft tissue destruction, but in the chronic form, conservative long antibiotic therapy may achieve results comparable to those of revision surgery combined with shorter antibiotic therapy after clinical selection of patients to each treatment (Aragon-Sanchez et al. 2008, Lazaro-Martinez et al. 2014, Tone et al. 2015). The IWGDF recommends a 1–2-week and a maximum of 3–4-week antibiotic regimen (Lipsky et al. 2019). The presence of LEAD may both prolong the antibiotic regimen and cause the failure of conservative treatment (Zeun et al. 2015, Aragon-Sanchez et al. 2008). After surgery, only a short antibiotic regimen is recommended (Lipsky et al.2019).

Regarding osteomyelitis, conservative treatment can be considered in cases with no sepsis and no considerable soft tissue destruction, if the patient prefers nonsurgical treatment and tolerates a long-lasting antibiotic regimen. The high risks of surgery also favour conservative treatment (Lipsky et al. 2019).

Surgical intervention should be considered if osteomyelitis or an accompanying soft tissue infection is progressive, the bone is no longer covered by soft tissue or is severely destructed, long antibiotic treatment is not feasible, or the patient prefers interventional treatment and a shorter antibiotic regimen (Lipsky et al. 2019). Surgery aims at removing the infected bone. Minor amputations are frequently performed. In the absence of acute infection, some specialists prefer "conservative" surgery: arthroplasties, sesamoidectomies, bone curettages and metatarsal head resections. Corrective foot surgery, such as resection of bony prominences and tenotomies, can be performed at the same time (Aragon-Sanchez et al. 2015).

2.3.4.4 OUTCOME OF DIABETIC FOOT INFECTION

Severe infections are seldom cured without surgery (Tan et al. 1996). Delayed surgery may result in more proximal amputations (Faglia et al. 2006). Repeated operations are typical for infections, and the numbers of minor and major amputations are high (Nehler et al. 1999, Commons et al. 2015, Pickwell et al. 2015, Clerici and Faglia 2014). Severe infections frequently result in transmetatarsal (TMT), Lisfranc and Chopart amputations (Clerici and Faglia 2014, Troisi et al. 2016). However, at least in the US, the number of diabetic foot infections requiring in-hospital care has decreased. In 1996, 33.2% of diabetic foot infections resulted in a minor or major amputation, whereas the corresponding in 2010 was 17.1% (Duhon et al. 2015).

The incidence of amputation is related to the severity of infection (Lavery et al. 2007, Pickwell et al. 2015). Indeed, of 27 patients with a severe infection, 30% underwent a major (leg) amputation and 40% a foot-level amputation, whereas the respective figures for the 52 patients with 52 a moderate infection were 23% and 23% and for the 71 patients with mild infections 2.8% and 0% (Lavery et al. 2007). The combination of infection and ischaemia, in particular, predicts poor wound healing and an increased number of major amputations (Prompers et al. 2008, Cull et al. 2014, Armstrong et al. 1998, Spillerova et al. 2015).

Revascularisations are infrequently reported in patients with a diabetic foot infection. In a French multicentre survey, only 9% of the patients underwent revascularisation, even though roughly 50% of the patients had signs of LEAD (Richard et al. 2012). In contrast, a study from an Italian specialised centre reported 64 revascularisations on 65 patients with absent distal pulses out of a total 106 diabetic patients with deep infections and abscesses. One patient with no pulses underwent emergency above-the-knee amputation because of sepsis (Faglia et al. 2006). Later, the same centre reported 83 Chopart amputations, 31 because of an abscess and 32 due to wet gangrene. Of the total 83 limbs, 64 were ischaemic and underwent revascularisation. Of patients with and without CLTI, 28% and 26%, respectively, underwent a major amputation (Clerici and Faglia 2014).

2.4 TREATMENT OF SEVERE TISSUE DEFECTS

The incidence of severe DFU is not exactly known, but in survey covering all of the US from 2001–2010, 2.5 million hospital admissions for DFU were observed, which represented 0.6% of all hospital admissions. Of the DFU admissions, 16.5% were for amputations, 35% of which were major and 65% minor amputations. In 8.5% of the cases, the admissions were for revascularisation, 43.5% of which were open, 51.1% endovascular and 5.4% hybrid (Skrepnek et al. 2014). In another nation-wide American survey of 625.2 million emergency unit admissions during 2006–2010, 10 19 861 admissions were for diabetic foot ulcers (Skrepnek et al. 2015).

A remarkable number of ulcers, seen at specialised multidisciplinary diabetic foot centres and vascular surgical centres are deep and infected. In a Swedish cohort from a multidisciplinary diabetic foot clinic, 21% of the ulcers were grade Wagner 3, deep and infected at inclusion. Furthermore, 55% of the ulcers fulfilled Wagner 3 criteria at some point (Elgzyri et al. 2014). In the Eurodiale study, 35% of the non-ischaemic and 63% of the ischaemic diabetic ulcers reached beyond the subcutis. Moreover, 58% of the Eurodiale patients had an infection (Prompers et al. 2007).

Large tissue defects are due to osteomyelitis, an abscess or gangrene, which often lead to proximal foot amputations if not severe enough to necessitate a major amputation (Clerici and Faglia 2014). In a study of 210 diabetic foot infections with an abscess, 45% of the patients underwent TMT, Chopart or Lisfranc amputation. A further 8.5% underwent a major amputation (Faglia et al. 2012). In an American study, 16% of the minor amputations related to vascular reconstruction were ray amputations and 21% TMT amputations (Sheahan et al. 2005). In the Eurodiale study, 34% were ray amputations and 11% midfoot amputations (Van Battum et al. 2011).

In and Italian study, diabetic patients had a 19-fold risk of minor amputation compared to the general population (Lombardo et al. 2014). Diabetic patients with LEAD had a 3.4-fold risk of minor amputation compared to nondiabetic patients who had been admitted to hospital due to LEAD (Hong et al. 2011).

2.4.1 REVISIONS AND MINOR AMPUTATIONS

Surgical debridement or wound revision comprises operations in which dead tissue, including bone, scar and debris, is removed with instruments, leaving vital tissue intact. Depending on the extent of the procedure, it can be performed at the bedside or in a surgical theatre. Amputations and corrective resections are usually reported separately from debridements and revisions.

In an Italian single-surgeon material of 1,407 infra-inguinal vascular reconstructions, 14% and 17.6% of the feet of a total of 705 diabetic patients and 10.1% and 12.9% of the feet of a total of 702 nondiabetic patients were preoperatively drained or debrided, respectively. Within a 30-day recovery period, diabetic patients underwent debridement significantly more often than non-diabetic patients: 5.1% of the diabetic patients needed drainage and 21.4% debridement, whereas the respective rates were 3.4% and 9.5% for nondiabetic patients. (Ballotta et al. 2014). The indication for revascularisation was ulcer in 41% of the diabetic patients and in 35% of the non-diabetic patients, while gangrene was the indication in 39% and 34% and rest pain in 19.1% and 31.5% of the diabetic and non-diabetic patients, respectively (Ballotta et al. 2014). In a cohort of 701 plantar forefoot ulcers, 558 healed without amputation below or above the ankle. Foot surgery was performed on 172 (30%) of the patients whose ulcers healed. Revision was enough in 70% of the patients, and 30% needed resection . Only one patient out of 172 received a skin graft (Örneholm et al. 2015).

Minor amputations of the foot include toe, ray and TMT amputations as well as Lisfranc amputation between the tarsal and metatarsal bones, and Chopart amputation in which the calcaneus and talus remain after removal of tarsal bones. Amputations in emergency situations may be performed with a freestyle approach – in other words, removing all non-vital tissue and leaving only viable tissue not adhering to the classical amputation levels.

In non-infectious circumstances, the aim is usually primary closure, but in infectious circumstances, the foot or toe amputation wound is commonly left open. It may be either closed later or left open to heal with conservative means (Berceli et al. 2006). Repeated debridement procedures and foot-level reamputations are frequently needed (Berceli et al. 2006, Beaulieu et al. 2015, Kono and Muder 2012, Blume et al. 2007). Negative wound pressure therapy probably promotes healing of open surgical wounds after partial foot amputations (Armstrong and Lavery 2005).

Following revascularisation on 554 patients for CLTI, the ulcers healed in 440 patients. Ninety-three out of 440 diabetic patients had toe or ray amputations and 254 a TMT amputation. Neither minor nor major amputation was necessary in 93 of the 440 patients: 35 healed with dressing changes, 30 needed split thickness skin graft (STSG), 16 had ulcerectomies and 12 had bone removals (Faglia et al. 2009).

In another study a toe amputation rate of 19.8%, a TMT amputation rate of 7.7% and a major amputation rate of 2.5% were observed after revascularisation among diabetic patients and the corresponding rates of 16.2%, 6.3% and 1.3%, respectively, among nondiabetic patients (Ballotta et al. 2014).
In the US, mortality has been reported to be 17.0%, 29.1% and 49.0% at 1, 3 and 5 years after initial minor amputations, respectively (Glaser et al. 2013).

2.4.2 SPLIT THICKNESS SKIN GRAFT

STSG is placed on granulation tissue or muscle, whereas tendon and bone are an unfavourable bed for STSG.

As a procedure, skin grafting is simple and can often be performed under local anaesthesia even in the office. Skin grafting may be advantageous regarding healing times and the length of hospital stay. Healing in diabetic patients was achieved in an average of 28 days after split-thickness skin grafting compared to 122 days after conservative treatment. The mean hospital stay also decreased by 12 days. (Mahmoud et al. 2008.) According to a review article, 65%–95% of the DFUs were 90% covered by the primary split-thickness skin graft within 2 to 8 weeks, depending on the cohort. The surface area of the ulcers varied from 1 cm^2 to 600 cm^2 (McCartan et Dinh 2012).

The success rate of STSG in diabetic patients has been reported to be similar compared to non-diabetic patients with chronic lower leg ulcers of considerable size (66.3 cm^2± 87.5 cm^2 in diabetic and 116.3 ± 216.2 in non-diabetic patients). An endovascular or open revascularisation preceded skin grafting in 37 of the 94 patients in the cohort. Of ulcers, 67% were plantar. Primary healing succeeded in 44/66 (67%) ulcers among diabetic patients and in 21/28 (75%) ulcers among nondiabetic patients during the median 6.5-month (0.5-52) follow-up. The mean ulcer healing time in successful cases was 7.2 ± 4.7 weeks in diabetic patients and 8.8 ± 6.5 weeks in nondiabetic patients, with no significant difference between the groups. (Rose et al. 2014.) In another study, in 66 out of 83 consecutive diabetic patients, a foot-level amputation was covered with STSG (Ramanujam et al. 2010). All but four had a prior infection. The median time to complete epithelisation was 6.9 weeks (1.7–31.5 weeks): 6.4 weeks in patients with uneventful healing and 9.5 weeks in 29 patients with complicated healing. Twenty-three needed regrafting and 21 another procedure, such as drainage of an abscess or resection of bone in addition to regrafting.

2.4.3 LOCAL FLAPS

Literature concerning local flaps in ischaemic diabetic feet is scarce. In a systematic review, a lack of high-quality evidence on the treatment of diabetic foot tissue defects with local flaps was observed (Ramanujam et al. 2018). According to the review, 76% of the ulcers healed during an average of 2-year follow-up. However, the material was heterogeneous. The publications included in the review were not focused on the role of vascular disease or other comorbidities. The largest cohort presented 67 patients with a deep ulcer, an ulcer on a bony prominence or recurrent ulcer which was revised and covered with a local random flap in a single operation. The ulcers were non-infected and

$tcpO_2$ was over 30 mmHg. Nine patients had undergone revascularisation. At 20 weeks, 96% of the ulcers had healed. The most common postoperative complications were wound dehiscence (18%), postoperative infection (12%), slough (9%), fracture and the recurrence of Charcot foot (6%). Fifty-four percent of the patients had no complications. A history of revascularisation or non-palpable pulses were not associated with healing. However, the cohort was small. Only the depth of the ulcer was significantly associated with healing and the mean number of bed days (Blume et al. 2002).

Pedicled perforator flaps and local random flaps alike tend to have a high risk of failure in patients with DFU and LEAD (Baumeister et al. 2003, Koh et al. 2018). However, distally based musculus peroneus brevis flaps were successfully used for covering heal ulcers in diabetic patients with only the fibular artery open in the leg (Nguyen et Rodriguez-Collazo 2019). Concentrated bone marrow aspirate, negative pressure wound therapy (NPWT), bilayer wound matrix, and external fixation were used as adjuvants. STSG was delayed. All flaps survived the 18-month follow-up.

A study comparing pedicled muscle flaps and FTT found no difference in wound healing, flap success or leg salvage between diabetic and non-diabetic patients (Ducic et al. 2011). On the contrary, healing times were longer and reoperations performed more often, and long-term survival was shorter in diabetic patients. However, the report only included a cursory examination of vascular disease – adequate vascular supply was required, and 9 revascularisations were performed during the study period, but more details on the presence of vascular disease in the study population were not given.

2.4.4 OTHER TREATMENTS

In complex ulcers, multiple methods and repeated procedures are typically necessary in order to achieve healing (Nguyen et Rodriguez-Collazo 2019). In a specialised centre in the US, the most frequent methods used for treating ulcers in diabetic Charcot feet were skin substitutes (32%) and skin grafts (21%). Primary closure was attempted in 15% and delayed closure in 18% of the patients. Furthermore, local flaps were used in 8% and free tissue transfer in 7% of the ulcers. Fifty percent of the ulcers healed, and 32% of the patients underwent major amputation during follow-up. (Sinkin et al.2015.)

Many promising methods for the treatment of DFU with or without LEAD have been suggested. Yet, little convincing proof of the efficacy of such methods as growth factors, skin substitutes, engineered biological wound dressings or HBO treatment has been published (Game et al. 2016, Conte et al 2019). According to a systematic review, some evidence exists on the benefit of hyperbaric oxygen therapy in healing among diabetic patients with ischaemia (Stoekenbroek et al. 2014). A pooled analysis showed that skin substitutes may be advantageous in total closure of a DFU. However, the role of

ischaemia was not discussed (Santema et al 2016). NPWT may increase the wound healing rate and reduce the healing time in postoperative wounds and DFU (Liu et al.2018). Intermittent pneumatic compression has been used safely on diabetic and ischaemic limbs. Bias in the studies reporting enhanced wound healing and improved limb salvage cannot be excluded (Conte et al. 2019). Offloading is an elementary part of the treatment of DFUs and should always be applied as appropriate (Bus 2016).

2.5 MAJOR AMPUTATIONS

Lower limb major amputation is usually defined as amputation above the ankle level. The established amputation levels are below-knee, through-knee, above-knee and hip exarticulation. The most common are below-knee and above-knee amputations. A life-threatening infection, irreversible acute ischaemia, intolerable rest pain and major tissue destruction of the foot due to gangrene, ulceration or osteomyelitis necessitate major amputation in a diabetic patient with LEAD. (Gooden et al. 1997.)

2.5.1 EPIDEMIOLOGY

In Finland, the incidence of major amputations has been decreasing according to population-based studies, but recent data has not been published (Ikonen et al. 2010, Eskelinen et al. 2006, Eskelinen et al. 2001) (Table 10). According to Finnish Institute for Health and Welfare statistics, the absolute number of all patients undergoing transfemoral amputation is quite stable (734 in 2008 and 783 in 2018), and transtibial amputations are slightly decreasing (417 in 2008 and 344 in 2018) In Europe, a major trend is decrease in the incidence of major amputations in diabetic patients (Lopez-de-Andres et al. 2015, Lombardo et al. 2014, Jørgensen et al. 2014). The incidences and incidence rates are not directly comparable between the studies. (Table 10).

The amputation rate in type 1 diabeticpatients seems to be higher than in type 2 diabetic patients. Type 1 diabetic patients tend to undergo amputation at a younger age (Lopez-de-Andres et al. 2015). In a Swedish population-based register study conducted in 2000–2004, below-knee major amputations were 19.5-fold more frequent and above-knee amputations 87-fold more frequent among type 1 diabetic patients than among the matched general population (Jonasson et al. 2008). According to a Scottish survey, the amputation rate was higher among type 1 than type 2 diabetic patients; 1.1% of type 1 s and 0.7% of type 2 diabetic patients had ever undergone a major amputation by 2016 (Scottish Diabetes Survey 2016). In Sweden, 11% of the women and 21% of men with type 1 diabetes had undergone a minor or major amputation by the age of 65 (Jonasson et al. 2008).

According to register-based population studies, the difference in rates of major amputation between diabetic and nondiabetic patients seems not to have changed

remarkably with time. Diabetic patients underwent 5,047 of the total 9,481 major amputations in Finland during 1997–2007 (Ikonen et al. 2010). In Southern Finland, 48% of the patients with a major amputation had diabetes, and 39% had both diabetes and CLTI in 2000 (Eskelinen et al. 2004). In a Finnish population-based study, the relative risk of major amputation was 7.4-fold (95% CI 7.2–7.7) for diabetic versus nondiabetic patients (Ikonen et al. 2010). In an Italian population, the age-, sex- and calendar-year-adjusted relative risk of major amputation was 6.4 in diabetic compared to nondiabetic patients (Lombardo et al. 2014).

The amputation rate of men with LEAD and diabetes was 1.5 times higher than men with LEAD alone and 5 times higher than men with diabetes without LEAD. In women, patients with LEAD with or without diabetes had amputation rates 2.5 times higher than patients with diabetes alone (Humphries et al. 2016a).

2.5.2 REAMPUTATION

Contra- and ipsilateral minor and major amputations are common (Glaser et al. 2013, Izumi et al. 2006). In a single institution, 144 patients who underwent above-knee amputation, 431 who underwent below-knee amputation and 1,140 patients who underwent a minor amputation were identified between 1998 and 2010. Seventy-seven percent of the patients had diabetes. Of those initially undergoing a major amputation, 8.5% had an ipsilateral major amputation and 11.5% a contralateral amputation by 5 years. Of those initially undergoing a minor amputation, 14% subsequently had an ipsilateral major amputation. Of those undergoing an initial minor amputation, 20% had an additional subsequent ipsilateral minor amputation by 5 years (Glaser et al. 2013.)

In Finland, 10% of 210 patients with major amputation had an ipsilateral above-knee reamputation, whereas 24% had a contralateral major amputation during the study follow-up period of 1998–2006. Fifty percent of the patients had diabetes (Remes 2010).

2.5.3 MORTALITY AFTER AMPUTATION

Mortality after major amputation is high. The patients are mostly in a poor general condition, not tolerating vascular surgery or being candidates for prosthetisation, some being bedridden. In a Finnish study, the one-month mortality was 21% and one-year mortality 52%. The annual risk was 7.4-fold compared to the general population in Turku (Remes 2010). In Southern Finland, 39% of patients with below-knee amputation and 61% of those with above-knee amputation died during the first year after major amputation. Roughly 50% of the patients had diabetes (Eskelinen et al. 2004). In the US, 19.2%, 48.7% and 61.3% died at 1, 3 and 5 years, respectively, after the initial major amputation (Glaser et al. 2013).

2.5.4 AMBULATION AFTER MAJOR AMPUTATION

Prosthetisation is successful only in a minority of patients after major amputation due to LEAD and diabetes. In a Finnish study, 119 out of 210 LEAD patients who underwent major amputation survived longer than one month and were discharged from the hospital, 68 to institutional care and 51 to their home. Thirty-nine (33%) of the discharged patients became prosthesis users (Remes et al. 2009).

Similar percentages were presented one year after major amputation in 2000 in Southern Finland. Twenty-two percent of all patients and 43% of those alive at one year had received a prosthesis. Of the below knee amputees alive at 2 months, 68% received a prosthesis within 1 year, compared to the 19% of above knee amputees. Ischaemia or diabetes were the cause in 95% of the amputations. (Eskelinen et al. 2004.) In Sweden, among 217 transtibial amputees with LEAD and a mean age of 77 years, 55% were fitted with a prosthesis (mean age 75 yrs) and, after a standardised rehabilitation programme, 64% achieved good function within six months, representing 31% of the original cohort. Fifty-one percent of the original cohort and 52% of the prosthetised patients had diabetes. (Johannesson et al. 2010.)

Predictors of prosthesis use after rehabilitation were good ambulation and functional independence, good cognition, absence of phantom pain and lower leg amputation. Risk factors for institutionalisation were old age, living alone, bilateral amputation or above-knee amputation. Similar reasons prevented prosthetisation. Furthermore, comorbidities such as hemiplegia, paraplegia, uraemia, dementia and alcohol abuse prevented prosthetisation. (Van Eijk et al. 2012.) In an American study, age > 60 years, bilateral amputation and end-stage renal disease were associated with the failure of ambulation in a retrospective review of 627 major amputations in 553 previously not completely bedridden diabetic and/or LEAD patients (Taylor et al. 2005).

Table 10. Incidence of major amputations in diabetic patients, with a comparison to non-diabetic patients.

Study	Patients	Incidence 1	Incidence 2	Population	Other
Winell et al. 2013	Finnish diabetic population	10.2 in 1997–2000	7.3 in 2004–2007	Finnish population 100 000 person years	First major amputation, standardised, population corrected incidence
Ikonen et al. 2010	Finnish diabetic population	94.4 in 1997	48.3 in 2007	Finnish diabetic population / 100 000	Age and sex standardised, first major amputation
Ikonen et al. 2010	Finnish nondiabetic population	10.7 in 1997	8.0 in 2007	Finnish nondiabetic population /100 000	Age and sex standardised, first major amputation
Alonso-Moran et al. 2014	Type 2 diabetic population of Basque country	0.1% in 2007	0.08% in 2011	type 2 diabetic population of Basque Country	Any major amputation
Lombardo et al. 2014	Diabetic population	114.5 in 2003	79.3 in 2010	Italian diabetic population /100 000	Persons with major amputation /year, crude rate
Lombardo et al. 2014	Non-diabetic population	4.8 in 2003	4.2 in 2010	Italian nondiabetic population /100 000	Persons with major amputation /year, crude rate
Lombardo et al. 2014	Diabetic population	48.4 in 2003	36.1 in 2010	Italian diabetic population /100 000	Persons with major amputation / year, Italian population age and sex standardised
Lombardo et al. 2014	Non-diabetic population	5.3 in 2003	4.2 in 2010	Italian nondiabetic population /100 000	Persons with major amputation /year, Italian population age and sex standardised
Kennon et al. 2012	Diabetic population	1.87 in 2004	1.11 in 2008	Diabetic population of Scotland/1, 000	
Kennon et al. 2012	Diabetic population	6.73 in 2004	443 in 2008	Population of Scotland /100 000	
Li et al. 2012	US diabetic population	11.2 in 1996	3.9 in 2008	diabetic population of US/1000	

Goodney et al. 2013	US diabetic medicare patients with LEAD		15.8 in2007–2009	/10 000 Medicare patients with LEAD	
Goodney et al. 2013	US nondiabetic medicare patients with LEAD		6.8 in 2007–2009	/10 000 US medicare patients with LEAD	
Humphries et al. 2016	Diabetic patients with LEAD	41 in 2005	31 in 2008	/1 000 000 total population in California	First major amputation
Humphries et al. 2016	Diabetic patients without LEAD	5 in 2005	6 in 2008	/1 000 000 total population in California	First major amputation
Humphries et al. 2016	Nondiabetic patients with LEAD	32 in 2005	17 in 2008	/1 000 000 total population in California	First major amputation
Humphries et al. 2016	Diabetic patients with LEAD	31 in 2009	31 in 2011	/1 000 000 total population in California	First major amputation
Humphries et al. 2016	Diabetic patients without LEAD	6 in 2009	6 in2011	/1 000 000 total population in California	First major amputation
Humphries et al. 2016	Nondiabetic patients with LEAD	17 in 2009	19 in 2011	/1 000 000 total population in California	First major amputation
Jørgensen et al. 2014	Male diabetic patients	0.25 in men over 50 in 2011	0.56 in men over 70 in 2011	/1,000 patient years	First major amputation, patients followed at Steno diabetes center
Jørgensen et al. 2014	Female diabetic patients	0.21 in women over 50 in 2011	0.41 in women over 70 in 2011	/1,000 patient years	First major amputation patients followed at Steno diabetes center
Larsson et al. 2008	Diabetic patients	16 1982–1986	6.8 1997–2001	/100 000 inhabitants	Two hospital districts, primary major amputations

US United States, LEAD lower extremity arterial disease.

2.6 REVASCULARISATION FOR CRITICAL LIMB THREATENING ISCHAEMIA (CLTI)

Revascularisation without delay down to an artery feeding the affected area the in a severely ischaemic leg with a tissue defect is crucial to prevent amputation in diabetic and nondiabetic patients alike (LoGerfo and Coffman 1984, Norgren et al. 2007, Noronen et al. 2017, Sheahan et al. 2005, Setacci et al. 2013). In the presence of less pronounced ischaemia, revascularisation is often necessary to promote healing, especially in diabetic patients with multifactorial aetiology, but little evidence exists on the proper timing of revascularisation. However, revascularisation is not always possible or advantageous for the patient. (Taylor et al. 2009, Chung et al. 2006, Nicoloff et al.1998, Oresanya et al. 2015.) Thus, we need to balance between the optimum of aiming at the best possible circulation and the consequences of procedures that are needed to reach this aim. Indeed, the recent ESVS guideline emphasises evidence-based revascularisation (EBR). The guideline proposal for a practical tool, PLAN, includes Patient risk estimation, Limb staging and a consideration of the ANatomic pattern of disease (Conte et a. 2019).

In addition to selecting the treatment path, including conservative treatment and amputation, according to the general condition of the patient, what is fundamental is that the delay is minimised and that after care and rehabilitation are maximised (Noronen et al 2017, Taylor et al. 2009, Nicoloff et al. 1998). The desired outcome and the patient's preference need to be defined: ulcer healing, avoidance of major amputation, survival, survival with a healed ulcer, independent living, independent mobility, good quality of life, etc. When aiming for one outcome, another can be threatened. Extensive procedures to overcome ischaemia or lengthy treatment to close a wound may threaten the patients' general condition or life (Nicoloff et al. 1998, Taylor et al. 2009 Seabrook et al. 1999). The characteristics (depth, size, infection) and location of the lesion, the technical possibilities to perform revascularisation (inflow, outflow, conduit), the patient's morbidity (general condition and procedure risks, mobility, nephropathy, dementia, coagulation disorders, oedema) have to be considered.

Factors not advocating revascularisation, open or endovascular, include an inability to use the leg for standing or moving to a wheelchair, an irreversibly poor general condition, a non-salvageable foot and life-threatening sepsis. High anaesthetic risks, severe nephropathy and poor technical conditions for revascularisation (inflow, outflow, conduit) should be weighed in relation to all risks. (Taylor et al. 2009, Oresanya et al 2015, Davies and El-Sayed 2015, Vierthaler et al. 2015, Suckow et al. 2012, Conte et al. 2019.)

Nehler et al. presented a good scheme to start with. If more than one of three fields – patient comorbidity, technical issues regarding revascularisation or ulcer characteristics – are compromised, the patient may not be a good candidate for vascular reconstruction (Nehler et al. 2003). In the end, the decision is individual.

2.6.1 SURGICAL REVASCULARISATION

Open revascularisation techniques comprise endarterectomy, angioplasty and arterial bypass. Endarterectomy, the removal of obstructive material and the inner layer of the artery through arteriotomy, is a common procedure on the femoral artery. Angioplasties, using a piece of vein or artificial material, are used to close an arteriotomy in order to prevent the narrowing of a vessel. Open angioplasty is also used to repair an obstruction in a vascular bypass graft. Occlusions throughout the arterial tree are suitable for bypass surgery, provided that an outflow artery exists. The TAP (target arterial path) concept and GLASS classification of the arterial disease pattern introduced by the Global Vascular Guideline (Conte et al. 2019) are practical tools also applicable in research for planning the treatment of vascular disease.

In diabetic patients, multilevel and distal disease are typical. Infrapopliteal and pedal reconstructions are usually necessary. Whenever proximal arteries are spared from occlusive lesions, inflow can be taken from the popliteal or, more rarely, from the crural artery (Saarinen et al. 2016). In a series of 1,032 bypasses to the ADP, inflow was achieved from the popliteal artery in 53% of the cases (Pomposelli et al. 2003). For a short bypass, a shorter vein is adequate, the operation time is often more limited, and graft occlusions may be less frequent than in longer grafts (Saarinen et al. 2016).

A single-segment great saphenous vein (SSGSV) in the best choice of graft for bypass surgery, followed by other autologous veins in the absence of SSGSV (Arvela et al. 2012). Autologous vein grafts have a good resistance to infections, which is a considerable risk in patients with a tissue lesion. In a consecutive series of bypass operations to treat CLTI from our clinic, a SSGSV was used in 74% of the operations (Arvela et al. 2010). Other options are the lesser saphenous vein and arm veins. A spliced vein is an alternative in the absence of a single-segment vein. In the absence a vein conduit, prosthetic material, homografts, umbilical vein or biosynthetic material, for example, are available.

Prosthetic material should be avoided in the presence of an infection. A prosthetic graft infection after bypass has been observed in 6% of patients with claudication, in 15% with rest pain, in 13% with an ulcer, and 33% with gangrene (Brothers et al. 2009). In a multivariate analysis of 496 prosthetic bypass grafts implanted during 2001–2010, female sex, diabetes mellitus, active infection and redo bypass were predictive for graft infection, and graft infection predicted major amputation (Siracuse et al. 2013). Foot infection was more common in diabetic than in nondiabetic patients undergoing vascular reconstruction for CLTI. Infection was associated with major amputation and the length of hospital stay (Mayor et al. 2018).

Poor runoff compromises the outcome. Among patients with poor run-off, 70% had graft loss, amputation or death six months after infra-inguinal bypass for ischaemic tissue loss (Seeger et al. 1999). In the absence of an outflow artery, a bypass to an FTT has been successful, in rare cases, without any other outflow (Tukiainen et al. 2000). Non-occlusive, obstructive lesions may not be good candidates for bypass surgery, as

the remaining flow steals from the graft, which easily occludes. Endovascular procedures are ideal for these lesions.

According to the national Finnvasc register, the 30-day graft thrombosis rate was 9% after vascular surgical revascularisation in diabetic patients and 10% in nondiabetic patients with CLTI (75% ulcer or gangrene) during 1990–1999 (Virkkunen et al. 2004). Diabetic patients seem to have at least as good an outcome for vascular grafts than nondiabetic patients (Wölfle et al. 2003, Ballotta et al.2014, Panneton et al. 2000).

Over time, more than 20% of bypasses occlude. The graft occlusion rate is lowest after bypass with a SSGSV conduit and is higher when arm veins, a spliced vein or prosthetic material is used (Conte et al. 2019, Arvela et al. 2012). In a series of 1,100 patients, 818 SSGSVs had better one- and three-year primary patency (74.4% and 67.1%, respectively) and limb salvage (88.9% and 86.9%, respectively) than 291 other vein conduits (53.7% and 43%; 83% and 77.2%), including lesser saphenous vein, arm vein and spliced vein conduits (Arvela et al. 2012). In infrapopliteal bypasses for CLTI, arm veins were superior to prosthetic grafts. The rimary patency at three years was 28.3% in arm veins, and 9.6% in prosthetic grafts, and the respective limb salvage 75.0% and 57.1 (Arvela et al. 2010).

Good long-term results are achievable even after inframalleolar bypasses. In a series of 352 inframalleolar bypasses for CLTI performed between 2002 and 2013 (prevalence of diabetes 69%), primary and secondary clinical patency was 81.0% and patency at 10 years 68.4%. The popliteal artery as the inflow artery (n = 194) was associated with superior patency in comparison to bypasses originating from the femoral artery (n = 158). The limb salvage rate at 1, 5 and 10 years was 78.6%, 72.0% and 67.2%, respectively. Limb salvage was equal in patients with and without diabetes (p =.460). The amputation-free survival rates at 1, 5 and 10 years were 58.4%, 29.8% and 12.8%, respectively (Saarinen et al. 2016).

2.6.2 ENDOVASCULAR TREATMENT

Endovascular treatment is performed through a percutaneous arterial puncture, ante- or retrograde to the target segment, usually under local anaesthesia and pain medication if necessary. Stenosed or occluded arterial segments are passed with a guidewire and dilated with a balloon catheter. Stents are placed to prevent recoil or to align the damaged arterial wall after dissection. Subintimal recanalisation, recanalisation devices, retrograde access and access via collaterals are methods that are evaluated for more successful recanalisation. Stents, drug-eluting stents, drug-coated balloons and stent prostheses are suggested to prolong the patency. (Conte et al 2019.) In diabetic patients with a tissue lesion, the technical success rate has been 85%–93% (Alexandrescu et al. 2009, Faglia et al. 2012, Uccioli et al. 2010, Jämsen et al. 2002, Ghoneim et al. 2014, Higashimori et al. 2016).

Most iliac artery revascularisation procedures are currently performed by endovascular means. The main obstacles for successful endovascular therapy are common femoral artery disease and long calcified lesions of the SFA and crural vessels (Gargiulo et al. 2011, Alexandrescu et al. 2009, Conte et al. 2019).

Due to long occlusions and heavy calcifications, the recanalisation and patency of the SFA still cause challenges (Conte et al 2019, Alexandrescu et al. 2009). Femoral bifurcation is not routinely treated by endovascular means, but techniques are evolving (Gargiulo et al. 2011, Thiney et al. 2015, Siracuse et al. 2017, Conte et al. 2019, Goueffic et al. 2017).

The popliteal artery is frequently treated with endovascular techniques. In the case of dissection or heavy calcification, stents may be considered but, as in the common femoral area, the risk of fracture and occlusion is increased by the mechanical stress. With the technical development of the equipment, crural and pedal vessels are balloon-dilated and recanalised routinely. However, the risks of failure increase with a decreasing size of the artery. Furthermore, the recanalisation of long calcified lesions in crural arteries may be impossible, or the result may be compromised. Bypass surgery may result in better flow if the patient tolerates surgery (Gargiulo et al 2011). The GLASS classification considers multilevel disease and combines femoropopliteal and infrapopliteal distribution of disease into three stages based on the estimated immediate technical failure rate and the leg-based patency at one year. In femoro-popliteal and infrapopliteal segments the length of diseased and occluded arterial segments and the severity of stenosis are graded. The inflow and inframalleolar disease are evaluated separately. (Conte et al 2019.)

The technical success rate of endovascular treatment limited to the infrapopliteal level was 95% in a series of 201 patients with DFU, (Fossaceca et al. 2013). The non-success rate for a below-knee procedure was 4% and for the SFA region 5.9% among 728 limbs with CLTI considered suitable for endovascular treatment (71% DM, 66% tissue loss) (Davies and El Sayed 2015). In the presence of an acute diabetic foot infection, the technical success rate has been somewhat lower, 85% (Setacci et al. 2013).

Restenoses and reocclusions occur frequently, in 20%–40% of lesions, after endovascular treatment. The rate depends on whether only observed symptomatic reocclusions or also asymptomatic ones caught in duplex surveillance are considered. Despite frequent restenosis, the limb salvage rates are quite good (Hinchliffe et al. 2016). During one-year follow-up, restenosis was observed in duplex surveillance in 80 out of 201 (39.8%) patients with DFU after endovascular treatment of infrapopliteal vessels. Sixty-six were symptomatic, with a recurrence or deterioration of ulcers (Fossaceca et al. 2013). Clinical restenosis (non-healing ulcer or recurrent rest pain) was observed in 23% of patients during a median of 6-year follow-up after endovascular treatment for CLTI in diabetic patients; 77% of the patients underwent a repeated endovascular treatment and 10% bypass surgery (Faglia et al. 2009). Restenosis, verified by duplex Doppler, occurred in 66/158 (42%) of the successfully treated lesions at one

year after endovascular treatment of below-knee arteries among 94 diabetic patients with ischaemic ulcers or gangrene who remained alive with the leg intact. The restenosis rate was 35% in stenotic and 53% in occlusive lesions. Two patients died, and 3 underwent major amputation before the one-year follow-up. In this study, only 3 patients underwent re-PTA, even though the minor amputation rate was 64% and the tissue lesions were evidently not minor ones (Ferraresi et al. 2009.)

2.6.3 HYBRID PROCEDURES

Hybrid revascularisation is a term used for a procedure containing both endovascular and open surgical elements. The unavoidable surgical part of the procedure is performed during the same session with the endovascular part. The advantage is that separate procedures are not needed, conversion to open surgery can easily be made, ulcerated areas can be treated endovascularly, the graft length can be optimised , and open surgery can be replaced by endovascular treatment. The combination of femoral endarterectomy and iliac PTA, or recanalisation and stenting is a typical hybrid procedure (Chang et al. 2008). A distal bypass or endovascular treatment of infrainguinal arteries may be included (Brewster et al. 1989). Infrainguinal bypass and outflow PTA is also a common 130620 procedure (Gargiulo et al. 2011). Quite extensive hybrid procedures have a long history (Lorenzi et al. 1991). Porter published a case report of two patients with combined intraoperative endovascular treatment of iliac lesions and a surgical revascularisation for limb salvage as early as in 1973 and Corey a series of fifteen patients in 1983 (Porter et al. 1973, Corey et al. 1983).

In multilevel disease, the proportion of hybrid procedures is higher than in local disease. Of 770 consecutive lower limb revascularisations (67% CLTI, 48% DM), 29% were opens, 57% endovascular and 14% hybrid revascularisations. Of multilevel reconstructions, in turn, 20% were open, 38% were endovascular and 43% were hybrid procedures (Dosluoglu et al. 2010).

2.6.4 SELECTION OF REVASCULARISATION MODALITY

Cautious individual consideration of the treatment of choice for each patient has been called for, regarding factors such as the general condition of the patient, the atherosclerotic disease pattern, the quality of the run-off vessel, graft material and local expertise (Spinelli et al. 2015, Conte et al. 2019). The BASIL trial gave no definitive answer to the question of whether an endovascular- or open-surgery-first strategy would offer a more favourable outcome (Bradbury et al. 2010). At present, a path towards evidence-based revascularisaton (EBR) is being searched (Conte et al. 2019, Farber 2019, Popplewell 2016). An endovascular-first strategy is not always feasible or optimal. Long calcified occlusions, or severe tissue destruction in the presence of an

acceptable outflow, vessel may be effectively treated with open-surgical revascularisation (Conte et al. 2019, Gargiulo et al. 2011). In contrast, open surgery predisposes the patient to general as well as to wound complications (Adam et al. 2005, Conte et al. 2019, Dosluoglu et al. 2012). However, the patency may be more durable after open surgery than after endovascular treatment and, on some occasions, the haemodynamic result better (Spillerova et al 2015). Consequently, in clinical cohorts, patients undergoing endovascular treatment tend to have higher morbidity, whereas patients with revascularisation tend to suffer from more extensive vascular disease and more severe tissue lesions (Dosluoglu et al. 2012, Taylor 2009). Indeed, revascularisation is a dynamic process where procedures are repeated or converted if necessary (Bradbury et al. 2010). In Helsinki, 394 consecutive patients with a combined 449 limbs with a foot ulcer, referred to the clinic due to a suspicion of CLTI during 2010-2011, were studied (Figure 3). Of these patients, 4.8% had type I and 56.6% type II diabetes. Revascularisation was scheduled for 233 (59%) patients, with a combined 248 (55%) limbs. The number of patients undergoing open surgery as a final treatment increased by 74% compared to the original strategy. (Noronen et al. 2017.)

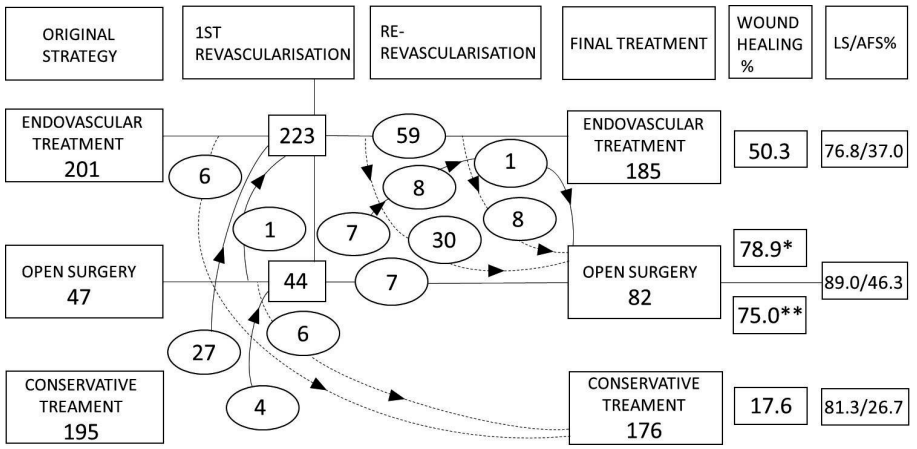

Figure 3. Treatment process of patients attending vascular surgical consultation in Helsinki. Reproduced with permission from Noronen et al. 2017. * Wound healing following secondary open surgery. ** Wound healing following primary open surgery.

In the US, endovascular treatment outnumbered open revascularisation in the treatment of ulcers in 2005 and of gangrene in 2006 (Hong et al. 2011). In an analysis based on the Healthcare Cost and Utilisation Project (HCUP) by the Agency for Healthcare Research and Quality in US, a very clear shift from open to endovascular

procedures was seen between 2001 and 2010. In diabetic patients, the number of open-surgical revascularisations was reduced from 11,500 to 6,900, while the number of endovascular treatments increased from 4,600 to 15,000. The number of combined open and endovascular procedures remained at 1,100-1,200 yearly. (Skrepnek et al. 2014.)

Whether a failed endovascular attempt deteriorates the results of open bypass surgery performed afterwards has been discussed (Conte et al. 2019). Graft patency and limb salvage have been poorer in patients with a prior failed endovascular revascularisation attempt before bypass surgery, when compared to patients without a prior endovascular attempt (69% DM) (Spinelli et al. 2015). However, confounding factors may play a role here, as the disease classification and run-off scores before and after the operations have not been adjusted, nor have the proportions of patients with rest pain only (Spinelli et al. 2015). However, a similar result was reported by Noronen and colleagues: limb salvage after a median of 26 months pf follow-up in patients with an initial open-surgical treatment was 96%, compared to the 82% (p=0.045) in patients with a failed endovascular treatment (Noronen et al. 2017).

2.6.4.1 FEASIBILITY OF REVASCULARISATION

A patient's feasibility for an operation and the technical feasibility of the procedure are perquisites for a successful procedure.

In Sweden, 801 out of 1,151 consecutive diabetic patients referred to a specialist foot clinic for ischaemic foot ulcers underwent angiography, and 345 were not considered feasible for revascularisation. Based on angiography, no revascularisation was technically feasible for 99 (12%) patientss; 50 (6%) had a poor general condition, and 33 (4%) had no vein graft available (Apelqvist et al. 2011, Elgzyri et al. 2014).

In the BASIL trial, 21 out of 228 patients assigned to open surgery underwent endovascular treatment and 10 had no intervention. Out of the 224 patients assigned to endovascular treatment, 4 were treated by open surgery and 4 had no interventions. (Bradbury et al. 2010.) In Helsinki in 2010, for 19% of patients initially scheduled for endovascular treatment, the intervention was converted to open surgery (Noronen et al. 2017).

In an American centre, the endovascular-first strategy was adequate in only 42% of the cases, with 47% of the patients needing bypass surgery and an additional 11% requiring a hybrid procedure. Diabetic patients had a higher probability of open revascularisation than nondiabetic patients. Trans-Atlantic Intersociety Consensus (TASC D) lesions required open surgery more often than less severe lesions. (Gargiulo et al. 2011.) In another American centre, patients who received endovascular treatment had more comorbidities, whereas those undergoing open revascularisation had more complex lesions (Dosluoglu et al. 2012).

Unfortunately, 1%–20% of all attempted revascularisations fail. In Sweden, an exploration revealed that open revascularisation was not feasible in 19/163 (15%) patients at a diabetic multidisciplinary clinic (Apelqvist et al. 2011). Furthermore, the absence of a target vessel prevented 1 and poor general condition 3 revascularisations (1%) among 360 consecutive diabetic patients referred for revascularisation (Faglia et al. 2012) In the BASIL trial, no functional graft was achieved for 5 (3%) patients when surgery was attempted. In one of the patients, the outflow artery was too calcified, another had no vein available, and for a further three no flow was achieved. In 20% of the 216 patients, endovascular treatment was not successful. In ten, the lesion could not be recanalised and in 18 the lesions were recanalised subintimally without re-entry to the lumen. Two patients could not tolerate the procedure from the beginning, and two vessels were perforated before recanalisation. In ten cases, immediate treatment-resistant thromboses prevented a successful procedure, and in one patient, stenosis detected by ultrasound was absent in angiography. (Bradbury et al. 2010.) Overall technical failure of endovascular treatment of below-knee arteries was observed in 11/201 (5.5%) patients due to long calcifications or a vagal reaction (Fossaceca et al. 2013).

2.6.4.2 FEASIBILITY OF REVASCULARISATION ACCORDING TO THE ANGIOSOME MODEL

Better flow in the ulcer area enhances ulcer healing in an ischaemic limb. Angiosome-targeted revascularisation is not always possible. Naturally, the vessel of the specific angiosome is often severely diseased, as the tissue defect is in that area (Zheng et al. 2016). In a study from Helsinki, all three arteries of the leg were retrospectively considered suitable for endovascular treatment in 12.4%, two in 54.7% and only one in 32.9% of the cases (Spillerova et al. 2016).

In another study, 16% of all endovascular attempts of tibial recanalisation were unsuccessful (Acin et al. 2014). Furthermore, out of these 101 infrapopliteal endovascular procedures in 92 diabetic patients with foot ulcers, 17 interventions resulted in indirect revascularisation without collaterals. Direct revascularisation to the ulcer angiosome was achieved in 46 procedures and indirect revascularisation through collaterals in 22 (Acin et al. 2014). In a further study, 31% of the patients had direct revascularisation to an angiosome, 26% were in the “without collateral” group, and an additional 43% in “indirect through collaterals” group (Zheng et al. 2016).

In 98 out of a combined 161 (60.9%) legs of patients (DM 66.5%) with CLTI and foot ulcers, angiosome-targeted below knee endovascular revascularisation was performed successfully (Spillerova et al. 2016). Angiosome-targeted revascularisation was considered possible in 129 out of 161 (80%) cases. However, in 23 cases, angiosome-targeted revascularisation failed (n=9) or was not attempted (n=14) because of a long occlusion, and another vessel was recanalised. In a further 8 cases, angiosome-targeted revascularisation was not attempted for an unknown reason. Only legs with successful

endovascular treatment for ischaemic tissue defects were included. (Spillerova et al. 2016.)

2.6.5 TIMING OF REVASCULARISATION

Delayed revascularisation deteriorates the outcome especially in diabetic patients (Noronen et al. 2017, Elgzyri et al. 2014, Sheahan et al. 2005). In a Finnish study, 394 consecutive patients with foot ulcers and a suspicion of ischaemia were referred to a vascular surgical consultation. Of these, 242 patients (61%) had diabetes. The limb salvage rate was significantly poorer in diabetic patients whose revascularisation took place later than two weeks after the referral, when compared to nondiabetic patients. Diabetic patients with a more than 2-week delay in treatment also had an increased risk of major amputation in a multivariate analysis on diabetic patients (Noronen et al. 2017). Similarly, in a Swedish study, diabetic patients with foot ulcers with a less than 8-week waiting time to revascularisation after evaluation at a multidisciplinary clinic had a better probability of healing without major amputation than patients with a waiting time exceeding8 weeks (Elgzyri et al. 2014). In urgent situations with a diabetic foot infection and ischaemia, rapid treatment has been favourable in terms of the outcome. In Italy, a protocol with urgent debridement and revascularisation within 24 hours was implemented. In the traditional group (n = 192), revascularisation was performed within a mean of 3 days (range 1–7 days) after debridement, whereas in the new protocol group (n = 183), revascularisation was always accomplished within 24 hours after debridement. The differences between the groups in six-month mortality, 11% vs 4%, and major amputations, 40% vs 25%, were statistically significant. The ulcer healing rate was low at six months: 8% and 21 %, respectively, with no significant difference. (Setacci et al. 2013.)

2.6.6 INCREASING REVASCULARISATION RATE – DECREASING AMPUTATION RATE

In the 1980s, a rapid increase in revascularisations for CLTI, including diabetic patients, took place in many countries. In population-based studies from Europe, Northern America and Australia, a decrease in major amputations has been observed concurrently with the increase in revascularisations (Luther et al. 2000, Lindholt et al. 1994, Gregg et al. 2014).

In Finland, an inverse correlation of increasing revascularisation rates, with infrainguinal or infrapopliteal reconstructions in particular, and decreasing amputation rates has been reported repeatedly as regards the general population (Luther et al. 1994, Luther et al. 2000, Eskelinen et al. 2004, Winell et al. 2006).

In a Finnish population-based register study on diabetic patients, the age- and sex-adjusted incidence of first major amputations and first vascular reconstructions were inversely correlated during 1997–2002 among the 14 largest hospital districts considering the number of diabetic patients. The inverse correlation was even stronger in infrapopliteal reconstructions. (Winell et al. 2006.)

In the American population during 1996–2011, the total number of revascularisations increased along with an increase in endovascular procedures from 138 to 584/100 000 Medicare patients, even though the number of surgical revascularisations decreased from 201 to 83 revascularisations /100 000 Medicare patients. Concurrently, the number of both above-knee and below-knee amputations decreased from 91 to 47 /100 000 and from 82 to 50 /100 000, respectively. (Goodney et al. 2015.)

2.6.7 PATENCY

Primary patency and assisted primary patency describe which proportion of bypasses or lesions treated with endovascular methods stay open without and with further assisting procedures (Table 11). Secondary patency includes bypasses that stay open with or without interventions for thrombosis (Table 12) (Rutherford et al. 1997). LBP (limb-based patency), a concept introduced by the Global Vascular Guideline, defines the patency of an arterial line down to the lesion independently of the method of revascualrisation (Conte et al. 2019). Graft material affects graft patency: single-segment vena saphena magna has the best primary patency, arm veins a less optimal patency, and prosthetic material the worst primary patency (Arvela et al. 2010, Arvela et al. 2012). No significant differences between diabetic and nondiabetic patients were observed in the rates of primary (65% and 46% vs 70% and 57%; log-rank test, P = .09) or secondary patency (76% and 60% vs 80% and 68%; log-rank test, p = 0.20) at 5 and 10 years of follow-up after vascular reconstruction for CLTI (Ballotta et al. 2014). Poor glycaemic control may decrease the patency (Singh et al. 2014).

Table 11. Primary patency (PP) of revascularisations in diabetic patients

Study	patients/ % DM	% tissue defect	1-yr PP	5-yr PP	10-yr PP
Berceli 1999; heel ulcers, 96 pedal bypasses	91%	100%	80%	62%	
Berceli 1999; forefoot ulcers, 336 pedal bypasses	96%	100%	81%	57%	
Pomposelli et al. 2003; 1,032 pedal bypasses	92%			57%	38%
Alexandrescu 2009; endovascular	176/100%	100%	62%		
Ballotta 2014	705/100%	80%		65%	46%
Ballotta 2014	702/0%	69%		70%	57%
Wölfle 2003; CLTI, femoro-distal bypass, 35% PTFE	94/100%	81%	66%		
Wölfle 2003; CLTI, femoro-distal bypass, 31% PTFE	117/0%	56%	56%		
Faglia et al. 2005; endovascular	CLTI 993/100%	87%		88% symptomless	

Table 12. Secondary patency of revascularisation in diabetic patients

Study	patients% DM	tissue defect %	1-yr secondary patency	5-yr secondary patency	10-yr secondary patency	limb salvage
Berceli et al. 1999; heel ulcers 96 pedal bypasses	91%	100%	85%	60%		94% 1 yr, 5 yrs 89%
Berceli et al. 1999; forefoot ulcers 336 pedal bypasses	96%	100%	85%	67%		94% 1 yr, 5 yrs 87%
Pomposelli et al. 2003; pedal bypasses	92%			63%	42%	78% 5 yrs, 58% 10 yrs
Alexandrescu et al. 2009; endovascular	176/100%	100%	80%			89%
Ballotta et al. 2014; bypass	705/100%	80%		76%	60%	5 yrs 88% 10 yrs 76%
Ballotta et al. 2014; bypass	702/0%	69%		80%	68%	5 yrs 91% 10 yrs 83%
Wölfle et al. 2003; CLTI , femoro-distal bypass, 35% PTFE	94/100%	81%	72%			1 yr 85%
Luther et al. 1997; CLTI, autologous vein	86/100%	61% in all 187	69%		53%	1 yr 69%, 5 yrs 51%
Luther et al. 1997; CLTI, autologous vein	101/0%	61% in 187	80%		69%	1 yr 81%, 5 yrs 81%

2.6.8 COMPLICATIONS

Since patients with CLTI have severe co-morbidities and often also severe coronary artery disease or cerebrovascular disease, the risk of death is increased compared to patients treated due to claudication. According to a systematic review, 30-day mortality after surgical and endovascular treatment in diabetic patients with tissue lesions was 0.5% (IQR 0%–4.3%) and 1.4% (IQR 0.8%–3.7%), respectively (Hinchliffe et al. 2016).

In a Swedish population-based register study, amputation-free survival was poorer among diabetic than in non-diabetic patients. Diabetic patients had an increased risk of both major amputation and death. Adjustment for demographic and risk factors had no significant effect on the result. Type 1 and type 2 diabetes were not reported separately (Malmstedt et al. 2008). Diabetic patients had significantly more major (death, systemic complications, graft thrombosis, major amputation; 16.7% vs 11.8%, p = .02) and minor complications (haematoma, infection, inguinal lymphocele; 9.7% vs 6.5%, p = .02) than nondiabetic patients after surgical revascularisation for CLTI. Regarding specific complications, the difference was not significant. The rate of wound infections was 0.8% in diabetic and 0.2% in nondiabetic patients. Dehiscence under haematomas and lymphoceles was classified separately. (Ballotta 2014.) Similarly, diabetes was associated with major adverse events following bypass surgery (Wallaert et al 2012).

In Finnish national register data, 30-day mortality after open surgical revascularisation among diabetic patients with CLTI was 4.5%, compared to the 3.4% among non-diabetic patients. Seventy-seven percent of the diabetic and 53% of the nondiabetic patients presented with tissue loss. Diabetic patients also had significantly more postoperative wound infections (15.7% vs 10.5%), below knee amputations (6.5% vs 3.3%), cardiac complications (8.8% vs 5.6%), cerebrovascular complications (2.1% vs 1.3%), and renal complications (1.6% vs 0.9%) than nondiabetic patients. (Virkkunen et al. 2004.)

2.6.9 NO REVASCULARISATION

The outcome of ischaemic ulcers without revascularisation is poor (Lepäntalo and Mätzke 1996). However, a tendency towards a better outcome in recent years has been observed (Abu Dabrh et al. 2015). Conservative care may preserve the functionality in the presence of an unhealing ulcer, when no immediate threat to the limb nor severe rest pain exists (Barshes et al. 2014). On the other hand, the benefit of revascularisation is not self-evident, as many studies report healing of ischaemic ulcers without revascularisation (Marston et al. 2006, Elgzyri et al. 2013, Apelqvist et al.2011).

Studying the effect of revascularisation on the outcome of patients with ischaemic ulcers is challenging (Bradbury et al. 2010). A trial comparing ulcer outcome after treatment for ischaemia to the outcome of leaving ischaemia untreated would be unethical. A comparison with historical series is impossible, as the setting was different compared to the present era. For instance, the general morbidity, medications and diagnostic modalities have evolved.

The Proportion of patients with an ischaemic foot ulcer who remain without revascularisation varies from 1% to 50% (Faglia et al. 2009, Elgzyri et al. 2013, Bradbury et al. 2010, Noronen et al. 2017). Frequently mentioned reasons for refraining from revascularisation are technical feasibility and poor general condition (Table 13). In a cohort of 544 patients with CLTI, 3.5% (n=20) possessed no outflow vessels for either endovascular or surgical revascularisation, whereas the general condition of seven patients (1.3%) prevented any invasive procedures (Faglia et al. 2009). In the BASIL trial, 386 out of 456 patients with severe ischaemia (rest pain or tissue loss) due to infra-inguinal disease were not randomised for the trial. The reason for not randomising were as follows: in 34% of the 456 cases, neither endovascular nor surgical treatment was considered a possible alternative, in 7% comorbidity precluded open surgery, in 3% the clinical situation had improved with medical therapy, and 4% were unable to give informed consent. Moreover, 16% were technically unsuitable for endovascular treatment and 20% for open surgical treatment. (Bradbury et al. 2010.) In a study conducted in Helsinki, 120/273 (44%) limbs of diabetic patients with CLTI (no limit values) and tissue loss and 75/176 (43%) limbs of nondiabetic patients were not revascularised at baseline, the major reasons being a poor general condition or bedridden status, and the assumption that the wound would heal without revascularisation. However, 17.5% and 13.3% of these, respectively, were revascularised later. In consequence, 37% of the patients had no revascularisation in the end (Noronen et al. 2017).

Not all patients who could benefit from revascularisation are probably offered one (Richard et al. 2011, Luther et al. 2000). In the 1990s, 20-fold variation was observed in infrapopliteal reconstructions and 30-fold variation in infrapopliteal endovascular treatment between different regions of Finland. Both diabetic and non-diabetic patients were included (Luther et al. 2000). A systematic stratification of patients (91% diabetes) in four treatment groups – revascularisation, primary amputation, palliative care, and conservative management without revascularisation – resulted in complete wound healing in 73% of the conservatively treated cases within a mean of 4.1 months. A revascularisation more than six months from enrolment was performed on 12% of the patients. The leg was preserved in 90% of these at four years. (Possagnoli et al. 2017.)

Table 13. Reasons for not revascularising, % of not revascularised patients.

	Spontaneous healing	Major amputation	Poor condition	Technically impossible	Lack of consent
Elgzyri et al.2013	16%	4%	28%	10%	17%
Noronen et al. 2017 nonDM	71%	7.5%	13%	6.7%	1.7%
Noronen et al. 2017 DM	47%	4%	47%	2.7%	0%
Apelqvist et al. 2011 no angio	13%	5%	41%		13%
Apelqvist et al. 2011 no revasc	7%	1%	17%	44%	10%
Bradbury et al. 2010	3%		7%	34%	4%
Faglia et al. 2009			1%	3,6%	
Marston et al. 2006			78%	14%	8%

2.7 FREE TISSUE TRANSFER (FTT) IN THE DIABETIC FOOT

2.7.1 HISTORY

The microvascular FTT technique was introduced in the 1970s along with the fast development of microsurgical techniques: microscopes, instruments and suture materials. Previously, in the 1960s, transfers of bowel segments and autotransplantations of the extremities and digits had been performed successfully (Seidenberg et al. 1959, Kleinert et al. 1963). The tissue lesions of the first human FTT patients were mostly caused by trauma or cancer. The first successful case was probably published in 1972. An omentum was used to cover a traumatic lesion on the scalp (McLean and Bunke 1972). Free skin flaps such as a groin flap, deltopectoral flap and dorsalis pedis flap soon became popular (Taylor and Daniel 1973, Harii et al. 1974). The free musculocutaneous flap was introduced in the late 1970s (Harii et al. 1976, Hill et al. 1978). In the mid-1980s, the technique was successfully applied to ischaemic and diabetic foot lesions (Briggs et al. 1985). Since then, dedicated centres in Europe, the US and Asia have published several series on the treatment of diabetic and ischaemic lesions with FTTs.

2.7.2 INDICATIONS

Generally, in large series of microvascular flaps, the most common indication in the lower extremities has been trauma. In a series of 231 microvascular flaps, the indications were acute (n = 105) or chronic (> 30 days) trauma (n = 59) and postoperative complication (n = 26), while 18 (8%) patients had a chronic wound and 15 (6%) had undergone oncologic resection. Thirty-five (15%) of the patients had diabetes, and 7 patients (3%) underwent revascularisation. (Cho et al. 2016.) Almost without exception, preventing major amputation has been the indication for FTT in the published series of patients with diabetes or LEAD (Moran et al. 2002, Tukiainen et al. 2000, Randon et al. 2010, Huang et al. 2014, Oh et al. 2013, Briggs et al. 1985, Oishi et al. 1993, Czerny et al. 2004, Karp et al. 1994, Gooden et al 1997, Hong et al. 2017, McCarthy et al. 1999, Shestak et al. 1990, Cronenwett et al. 1989) (Table 14). The distribution of tissue defect locations vary between the studies. Notably, in many studies, the proportion of heel ulcers is high (Table 15). No specific criteria for the threat of amputation – such as size, toe or ABI measurements – are given, but the decision to operate has relied on clinical judgement, individually for each patient.

Table 14. Patient and FTT a revascularisation operation details.

Author, year/ N	Age	Male	Smoking	DM	Flap	Revasc.	uraemia/RT
McCarthy 1999/ 21	59 (40-73)	95 %	48%	86%	LD 5, RA 5, omentum 5, gracilis 2, RFA 3, scapular 1	21 open	
Tukiainen 2000/29	62 (43-85)	69 %	7%	83%	LD 20, 7 RA, RFA 1, TFL 1, gracilis 1	29 open	28%/14%
Moran 2002/ 75	60			76%	RA 35, LD 15, RFA 24, scapular 3, omentum 2	61open (81%)	27%*/ X
Randon 2010/ 55	64 (42-80)	76 %	36%	100 %	RA 44, LD 5, ALT 3, serratus anterior, lateral arm	55 open	X/5%
Gooden 1997/ 26	60 (24-76)	62 %	50%	90%	RA 9, RFA 8, LD 7, scapular 3	17 open (65%)	33%/X
Huang 2014/ 24	71	42 %		100 %	LD and RA	24 (endo)	25%/X
Oh 2012/121	55 (26-78)		35%	100 %	ALT 90, SCIP 20, AMT 5, UMT 3	9 open+5 endo (11,5%)	35%/8 %
Lee 2014/33	60	91 %	45%	100 %	ALT 19, TAP 9, gracilis 5	33 open or endo	

age mean (range), * renal insufficiency and uraemia, RT renal transplant, open: open revascularisation, endo: endovascular revascularisation

LD, latissimus dorsi muscle flap; RA, rectus abdominis muscle flap; RFA, radial forearm fasciocutaneous flap; TFL, tensor fasciae latae muscle flap; ALT, anterolateral thigh perforator flap; SCIP, superficial circumflex iliac perforator flap; AMT, anteromedial thigh perforator flap; UMT, upper medial thigh perforator flap; TAP, thoracodorsal artery perforator flap

As a more specific indication, tissue lesions with the joint, bone or tendon visible are often mentioned (Randon et al. 2009, Gooden et al. 1997, Tukiainen et al. 2000, Lee et al. 2014, Karp et al. 1994, MCCarthy et al. 1999). The background factors often include

osteomyelitis (Hong et al. 2017, Gooden et al.1997, Moran et al. 2002, Cronenwett et al. 1989), a plantar defect (Cronenwett et al. 1989, McCarthy et al. 1999, Gooden et al. 1997, Randon et al. 2010, Vermassen and van Landuyt 2000), infection (Hong et al. 2017), foreign material (Tukiainen et al. 2000), or wound healing problems after an open fracture (Tukiainen et al. 2000). An attempt with an STSG or local flap has often been made previously (Cronenwett et al. 1989, Gooden et al. 1997). As regards a previous or present revascularisation, flaps have been used to cover distal anastomosis in the tissue defect area (Gooden et al. 1997, Tukiainen et al. 2000), necrotic defects in the distal anastomosis site due to vascular graft infection (McCarthy et al. 1999, Tukiainen et al. 1998), ischaemic muscle necrosis after vascular reconstruction and fasciotomy (Tukiainen et al. 2000), and necrotic vein harvesting wounds (Gooden et al 1997). FTTs have been shown to increase flow in the vascular graft (Lorenzetti et al. 2001). They have been used as a sole outflow for a graft in the absence of local outflow artery (Shestak et al. 1990, Tukiainen et al. 2000, Moran et al. 2002, Mimoun et al. 1989, McCarthy et al.1999). Even neovascularisation in the native tissue via the FTT has been suggested (Mimoun et al. 1989, Randon et al. 2010, Mätzke et al. 1998). The locations of the tissue defect in various series is presented in Table 15.

To qualify as a candidate for FTT, the patient should be ambulatory, at least being able to step on the foot when moving into a wheelchair (Gooden et al. 1997, Tukiainen et al. 2000, Oishi et al. 1993). Some studies report many patients with a previous major contra-lateral amputation (Gooden et al. 1997, Moran et al. 2002, Tukiainen et al. 2000, Serletti et al. 1993). Cultural reasons may favour FTT over amputation, not necessarily even for the sake of mobility but simply to preserve the leg (Huang et al. 2014). Good cooperation by the patient is required for the procedure. A general condition allowing an operation that lasts several hours and involves substantial bleeding, as well as a lengthy recovery period, is obligatory (Oishi et al. 1993). Along with the experience accumulated from many centres, patients with severe nephropathy have often been excluded from this kind of treatment at present. Furthermore, in bedridden patients, as well as patients with a poor prognosis of survival, poor predicted outcome or severe neurologic impairment, major amputation is indicated in lieu of FTT and vascular reconstruction (Randon et al. 2009).

Table 15. Location of the tissue defect in patients with FTT. An ulcer may involve more than one location.

Author	N flaps	forefoot	heel	plantar	leg	dorsum, ankle
McCarthy et al. 1999	21	-	52% (or plantar)	52% (or heel)	-	-
Tukiainen et al. 2000	29	40%	43%	-	3%	-
Illig et al. 2001, Moran et al. 2002	65 (2001) 79 (2002)	13% (2002)	19% (or plantar, 2002)	37% (2001) 19% (or heel 2002)	17% (2001) 22% (2002)	46% (2002)
Randon et al. 2009, Randon et al. 2010,	76 (2009) 55 (2010)	44% (2009) 51% (2010)	29% (or plantar 2009) 40% (2010)	29% (or heel 2009) 9% (2010)	12% (2009)	15% (2009)
Gooden et al. 1997	26	-	44%	11%	30%	15%
Huang et al. 2014	24	27%	19%	27%		23%
Lee et al. 2014	33	-	12%	9%	-	d:55%, a:24%
Fitzgerald O'Connor 2011 (review)	399	30%	24%	10%	24%	12%

2.7.3 FTT AND CLTI

In CLTI, the proportion patients who undergo FTT surgery varies between 0% and 10% at specialised clinics. A survey from an amputation prevention clinic describes the podiatric as well as vascular procedures performed in 89 patients to save a limb threatened with amputation due to neuroischaemic ulcers. Of the patients, 68% had diabetes. A total of 151 podiatric, 86 vascular and 8 plastic surgical interventions were performed. Two (2.4%) of them were FTTs. (Vartanian et al. 2015.) In another study, 585 procedures for tissue defects on 544 patients with lower extremity ischaemia in 1992–1996 included 266 infra-inguinal bypasses, 66 major amputations, 226 minor amputations or operative debridements, and 27 (5%) myofasciocutaneous FTTs. (Gooden et al. 1997). Furthermore, 55 diabetic patients underwent FTT during same time period, as infrapopliteal vascular reconstructions were performed on 248 diabetic patients and major amputations on 295 patients (Randon et al. 2010). In Seoul, Korea,

71 out of 287 (25%) diabetic patients who were evaluated for limb salvage underwent perforator flap reconstruction. Of these, 216 were considered unsalvageable (Hong 2006). In Helsinki University Hospital, the treatment for 733 patients with CLTI was vascular reconstruction in 66%, primary amputation in 19% and conservative treatment in 15% of the cases. FTT was applied in 15 cases (Lepäntalo and Mätzke 1996).

2.7.4 FLAPS

Evidence on the applicability of different free flaps in the diabetic foot is lacking. The current practice leans on case series and expert experience. An almost endless choice of flaps is available. While selecting the flap for a diabetic foot, the size, depth and location of the defect and the presence of atherosclerosis are evaluated. The size and volume of the flap, the flow in the flap, the length and atherosclerosis of the pedicle, the tolerability to pressure and shear stress, as well as donor site morbidity and the complexity of the elevation of the flap are considered. According to published series, most centres use a variety of flaps that are appropriate for individual cases of diabetic and ischaemic foot defects (Table 16). Microvascular muscle flaps (latissimus dorsi, serratus, rectus abdominis) and microvascular fasciocutaneous radial forearm flaps have been popular in treating DFU (Tukiainen et al. 2000, Moran et al. 2002, McCarthy et al. 1999, Randon et al. 2009, Fitzgerald O'Connor et al. 2011). Muscle is well vascularised and optimal for filling in cavities, and the pedicle size is moderate. High flow is considered advantageous for vascular bypass graft patency (Lorenzetti et al. 2001). However, a muscle flap can be bulky and cause donor site problems (Knott et al. 2015).

More recently, good results have been reported with microvascular perforator flaps (Hong 2006, Randon et al. 2010, Oh et al. 2013, Fitzgerald O'Connor et al. 2011). The advantages of perforator flaps are the good cosmetic fit, an abundance of different flap options and the fact that, in the case of failure, the underlying muscle is often usable (Koh et al. 2018, Goh et al. 2015). The disadvantages of microvascular perforator flaps are the time-consuming elevation and small size of the pedicle. The flow in the flap is low and tissue needed to fill cavities is meagre compared to muscle flaps. Large series on the lower leg include ALT (anterolateral thigh perforator) and SCIP (superficial circumflex iliac artery perforator flap), which have been used for ischaemic and diabetic foot defects, among other purposes (Koh et al. 2018, Goh et al. 2015). In a series of anterolateral thigh perforator flaps, sensate flaps were used in diabetic feet, in which preserved sensation was confirmed by filament testing preoperatively (Hong 2006). The sensation returned in four months.

The omentum has been used occasionally, especially in extensive defects (McCarthy et al. 1999, Mazzaferro et al. 2018).

Table 16. Characteristic of different types of FTT. Reproduced with permission from Lepäntalo et al. 2004.

Flap	Outflow ml/min	Athero-sclerotic pedicle	Harvest compli cations	Anaesthetic considera tions	Patient position	Size
latissimus dorsi	20–50 ml/min	+	+	+++	lateral/ dorsal+upper body twist	+++
rectus abdominis	10–20 ml/min	++	++	++	dorsal	++
gracilis	5–15 ml/min	+++	-	-	lateral	+
serratus	5–15 ml/min	+	-	+++	lateral	+
radial forearm	4–10 ml/min	+	++	±	dorsal	+
anterior thigh	10–20 ml/min	++	+	-	dorsal	++
omentum	20–30 ml/min	+	++	+++	dorsal	++

2.7.5 FTT TECHNIQUE IN THE ISCHAEMIC DIABETIC FOOT

FTT and vascular reconstruction are possible to perform with simultaneous or staged operations. Two teams working at the same time reduce the operating time (Randon et al. 2009). The absence of scarring in a simultaneous operation facilitates dissection and performing venous and arterial anastomoses (Moran et al. 2002, Randon et al. 2009). A staged operation may ensue when the severity of the defect is revealed after revascularisation and debridement, often multiple. However, a staged operation may be preferred, as small deep veins tend to dilate after revascularisation, which is advantageous for the microvascular venous anastomosis.

Debridement and the final evaluation of the defect initiate the operation. In a large series from Belgium, 64% of the patients needed minor revision or amputation (Randon et al. 2009).

Subsequently, flap elevation and vascular reconstruction may be performed simultaneously in clean fields. The ipsi- or contralateral vena saphena magna is the preferred vascular graft (McCarthy et al. 1999, Tukiainen et al. 2000). Good-quality arm veins (McCarthy et al. 1999, Tukiainen et al. 2000), the vena saphena parva

(McCarthy et al. 1999), and very seldom a composite graft (McCarthy et al. 1999, Tukiainen et al. 2000) are secondary options. In the absence of a vein graft, PTFE or cryopreserved allografts have been used (Tukiainen et al. 2000, Randon et al. 2009). The thoracodorsal artery may sometimes replace a venous graft (Malikov et al. 2009).

Inflow to the flap is obtained via the vascular graft or tibial vessel closest to the defect site (Moran et al. 2002). Venous drainage is anastomosed to the tibial vein (McCarthy et al. 1999). The anastomosis of the flap artery is made end-to-side to the vein graft (McCarthy et al. 1999, Moran et al. 2002, Oh et al. 2013, Tukiainen et al. 2000), directly to the flap (McCarthy et al. 1999, Tukiainen et al. 2000) or to a native artery (Moran et al. 2002, Tukiainen et al. 2000). The anastomosis can be made end-to-end to a native artery branch (Oh et al. 2013), end-to-end to a native artery stump (Oh et al. 2013), or side-to-side to a GSV bypass or distal native artery (Randon et al. 2009). Especially large muscle flaps enhance flow (Randon et al. 2009, Lorenzetti et al. 2001) (Table 16). Muscle and omentum flaps need coverage with a skin graft, whereas myocutaneous and fasciocutaneous flaps include the skin. The mean duration of a simultaneous operation has varied between 5 and 7 hours, range 4–13 h (McCarthy et al. 1999, Tukiainen et al. 2000, Moran et al. 2002, Randon et al. 2010, Malikov et al. 2009).

A combined endovascular revascularisation and FTT is described in a series of 26 flaps in 24 patients with diabetic Wagner 3 and 4 lesions. The patients were treated with PTA of infrapopliteal lesions and revision. A week later, a free vastus lateralis or rectus femoris free muscle transfer and STSG was performed. One perioperative death occurred. Two major amputations were observed at 6 and 21 months, respectively. (Huang et al. 2014.)

2.7.6 POSTOPERATIVE SURVEILLANCE AND AMBULATION

Intensive postoperative surveillance of the flap by means of hourly clinical assessment (inspection, temperature, bleeding) (Gooden et al. 1997, Randon et al. 2009) and Doppler auscultation (Randon et al. 2009) ensures the early detection and removal of vascular thrombosis, enabling flap salvage. The median hospital stay is long, in two large studies 32 and 48 days (6–113 days), respectively (Moran 2002, Randon 2009). Duplex Doppler surveillance of the vascular graft every three months has been standard during the first year after the operation (Randon et al. 2009, Tukiainen et al. 2000, McCarthy et al. 1999, Illig et al. 2001).

Bed rest is advocated for the first postoperative week (Tukiainen et al. 2000). Weight bearing is allowed 3–6 weeks postoperatively (Illig et al. 2001, Randon et al. 2009, Tukiainen et al. 2000, Hong 2006). Achieving bipedal ambulation takes from three weeks in the case of the most favourable non-plantar ulcers to up to twelve weeks in plantar ulcers (Czerny et al. 2004, Gooden et al.1997, Randon et al. 2009, Hong 2006, Illig et

al.2001). Independent ambulation was achieved by 65%–76% of patients at some point (Illig et al. 2001). Swelling needs to be avoided by light elevation of the extremity. After wound healing, compression stockings have been used for six months for remodelling (Randon et al. 2009, Hong 2006).

2.8 OUTCOME

2.8.1 ULCER HEALING

In chronic ulcers, the process of healing is disturbed. Wound healing consists of four phases: haemostasis, inflammation, proliferation and remodelling. Excessive inflammation, a decreasing division of fibroblasts, and alterations in bacterial flora are suggested factors in the background of impaired healing (Bosanquet et al. 2014). The healing of ulcers remains consistently undefined in clinical studies, and the frequency of control visits is seldom reported. Small epithelial defects may not be detected with the naked eye, or an unremoved eschar may cover them. Furthermore, ulcers may reulcerate soon after they have been assessed to be healed. Consequently, a Swedish study group considered ulcers healed after the skin has been intact for 6 months (Gershater et al.2009).

Series mostly from multidisciplinary diabetic foot clinics describe a worse outcome for neuroischaemic and ischaemic ulcers than for neuropathic ulcers. However, the level of ischaemia, revascularisation and the outcome of revascularisation remain ambiguous in many reports (Prompers et al. 2008, Jeffcoate et al. 2006).

In clinical work, no method is available for ensuring adequate circulation as regards healing. A small stabile ulcer rarely deteriorates acutely (Barshes et al. 2014). Indeed, spontaneous healing of ulcers in ischaemic feet is also known to occur (Marston et al. 2006). Revascularisation is probably not always necessary for the healing of small non-infected ulcers (Cull et al. 2014), but the probability of amputation increases with the depth and level of infection of the ulcers (Lepäntalo and Mätzke 1996, Cull et al. 2014).

The proportion of healed ulcers has been noted to decrease along with the severity of ulcer scoring performed after revascularisation (Cull et al. 2014). The scoring is based on the extent of the ulcer, the severity of ischaemia and infection. Thirty-seven percent of WIfI score 4 ulcers healed within 1 year, as opposed to 65.2% of WIfI 3, 78.1% of WIfI 2 and 92.5% of WIfI 1 ulcers. The limb salvage was 62.5% in WIfI 1, 76.7% in WIfI 2, 88.9% in WIfI 3, 97.3% in WIfI 1 ulcers. (Cull et al. 2014.) However, we do not have tools to exactly predict which ulcers heal or show no progress. Similarly, the complete healing of ulcers in 124 limbs of 98 patients with or without a minor amputation was observed in

79% of the limbs following angiosome-oriented endovascular revascularisation. Furthermore, 89% of Wagner grade 1–2 ulcers and 67% of Wagner grade 3–4 ulcers healed within 3 months. (Alexandrescu et al. 2008.)

2.8.1.1 ULCER HEALING IN COHORTS WITH DIABETIC ULCERS

Generally, 60%–75% of neuroischaemic or otherwise complicated ulcers heal, whereas the healing rate is over 80% for purely neuropathic ulcers treated in specialised diabetic foot centres. In the Eurodiale study, 69% of the ischaemic or neuroischaemic ulcers healed within one year, in comparison to the 84% healing rate of purely neuropathic ulcers (Prompers et al. 2008). When infection was present in an ischaemic ulceration, 64% of the wounds healed and 10% of the limbs underwent major amputation during one-year follow-up. On the contrary, in non-ischaemic limbs, the healing rate was 85% irrespective of infection.

In a cohort of 2,480 diabetic ulcers that were followed until healing or death in a Swedish multidisciplinary foot clinic, 65% healed primarily. The primary healing rate of neuropathic ulcers was 79.4%, whereas only 44.4% of neuro-ischaemic ulcers healed primarily. In legs with an ankle pressure less than50mmHg, 39% of the ulcers healed primarily. Of neuropathic ulcers, 7.1% resulted in minor and 2.4% in major amputation, and 11.1% remained non-healed at death, compared to the corresponding rates of 14.5% ,15% and 25.5 %, respectively, with neuroischaemic ulcers. (Gershater et al. 2009.) Other factors associated with ulcer healing are named in Table 17. The outcome of a subgroup of 701 consecutive patients with a single plantar forefoot ulcer between 1984 and 2012 was studied separately. Twenty-six percent had severe LEAD and 14% a deep infection of the foot. In 385 (55%) patients, the ulcer healed without surgery, in 173 (25%) after foot surgery, in 42 (6%) after minor amputation and in18 (3%) after major amputation, and 83 (12%) died with the ulcer unhealed. Thirteen percent (92/701) of the patients underwent revascularisation during the follow-up. Of these, 39 (42%) healed without surgery on the ulcer, 22 (24%) healed after ulcer surgery, 10 (11%) healed after minor amputation, 6 (7%) underwent a major amputation, and 15 (16%) died with the ulcer unhealed. (Örneholm et al. 2015.) A hospital-discharge-register-based survey from 1996–2000 covering the US showed that diabetic patients over 80 years had more complications of foot ulcers than nondiabetic patients: a respective 0.04% and 0.02% had a foot infection, and a respective 0.5% and 0.1% underwent toe amputation, a respective 0.2% and 0.01% underwent a foot-level amputation, and 1.2% and 0.3%, respectively, underwent a major amputation (Reed 2004).

In a British study involving 432 diabetic patients, 55% and 65.7% of foot ulcers of mixed origin healed by 6 and 12 months, respectively. Of the ulcers 27.8% and 11.6% were

unhealed at six and 12 months, 6.2% and 10.9% were unhealed at death, whereas 5.8% and 8% of the ulcers resulted in amputation, respectively. At 1 year, 45% of the patients were alive, ulcer-free and without amputation. (Jeffcoate et al. 2006.)

Table 17. Factors related to primary healing in all surviving neuroischaemic/ischaemic patients. (Reproduced with permission from Gershater et al. 2009).

Factor	Odds ratio	95% CI	p-value
Age 18–60 years	1.80	1.01–3.21	0.045
Age 71–80 years	1.70	1.14–2.52	0.009
Male sex	1.40	1.00–1.93	0.044
Living in own home	2.43	1.58–3.72	<0.005
Nephropathy	1.54	1.03–2.28	0.033
No uraemia	2.45	1.35–4.46	0.003
No previous amputation	2.30	1.23–4.29	0.009
Claudication	1.71	1.17–2.51	0.006
No pain	1.90	1.37–2.63	< 0.005
Single ulcer	2.17	1.44–3.28	< 0.005
Wagner grade 1 and 2	9.76	6.77–14.08	< 0.005
Wagner grade 1, 2 and 3	3.52	2.11–5.88	< 0.005

2.8.1.2 IMPACT OF REVASCULARISATION

The ulcer healing rate after revascularisation varies between 60% and 80% (Hinchliffe et al. 2016). In one series, complete healing of diabetic foot ulcers was achieved in 83% of patients after revascularisation by endovascular or surgical means. In 80% of the patients, healing was completed after a minor amputation. (Faglia et al. 2009.) Apelqvist

and colleagues describe the outcome of revascularisation in a cohort of 1,046 diabetic patients with ischaemic foot ulcers treated and followed up at a multidisciplinary clinic. PTA and vascular surgery increased the probability of primary healing in multivariate analysis (OR 1.77 and 2.05, respectively). Other factors related to primary healing were age, the severity of ischaemia, the extent of tissue destruction and the presence of comorbidity, such as heart failure and renal impairment. In 46% of endovascular cases, the crural arteries were treated, and 51% of the open-surgical reconstrucions had truncal or lower run-off. Healing without major amputation (primary healing and healing after minor amputation) occurred in 61% of 190 patients after vascular surgery, in 58% of 314 patients after PTA, in 46% of 297 patients after angiography without PTA, and in 47% of 345 patients without angiography. The median healing time was 27 weeks (1–292 weeks). The median follow-up time was 2 years (0.5–5) (Apelqvist et al. 2011) (Table 18).

Table 18. Outcome of diabetic patients with neuroischaemic diabetic foot ulcers. Reproduced with permission from Apelqvist et al. 2011.

		No angiography n=345		Medical treatment n=297		PTA n=314		Vascular surgery n=190	
	n	n	%	n	%	n	%	n	%
primary healing	415	127	37	96	32	121	39	71	37
minor amputation	184	36	10	43	14	60	19	45	24
major amputation	143	33	10	45	15	34	11	31	16
deceased	310	128	37	84	28	63	20	35	18
dropouts	60	14	4	21	7	21	7	4	2
unhealed	34	7	2	8	3	15	4	4	2

Even though a review by Hinchliffe et al. (2016) concludes that one method of revascularisation is not superior over another regarding outcome, a study from our clinic in Helsinki indicated that bypass surgery may have a better haemodynamic effect than endovascular surgery. In a retrospective cohort of 545 diabetic patients with CLTI and tissue loss (Rutherford 5and 6), who underwent infrapopliteal endovascular (PTA) or open surgical revascularisation between January 2008 and December 2013, 60.3% of the ischaemic wounds healed during 1 year of follow-up. The highest wound healing rate

was achieved after angiosome-targeted bypass (77%) and the worst after non-angiosome-targeted endovascular revascularisation (52%). When Cox proportional hazard analysis was adjusted for the number of affected angiosomes, direct bypass yielded the best wound healing (p = 0.003). (Spillerova et al. 2017.) Indeed, earlier studies report a similar outcome of bypass surgery regardless of the angiosome in relation to the location of the ulcer (Bergamini et al. 1994, Berceli et al. 1999).

2.8.1.3 ANGIOSOMES

Four recent meta-analyses reported better wound healing and limb salvage after angiosome-targeted versus non-angiosome-targeted revascularisation. One concerned endovascular treatment in diabetic patients, the others endovascular and open revascularisation of either infrapopliteal or any lower limb arteries (Jongsma et al. 2017, Chae et al. 2016, Bosanquet et al. 2014, Biancari and Juvonen 2014). One of the meta-analyses entailed a discussion on the limited benefit of angiosome-targeted open surgical revascularisation, as the least affected outflow vessel, irrespective of the angiosome, is usually selected (Jongsma et al. 2017).

A better ulcer healing rate of 75% among diabetic patients who underwent a combined 121 angiosome-targeted revascularisations compared to the rate of 45% among patients who underwent a combined 129 non-angiosome-targeted revascularisations was observed in a Finnish study. The result was confirmed by propensity score analysis. In the case of an ulcer involving multiple angiosomes, direct revascularisation was defined as one opened angiosome specific artery (Söderström et al. 2013.)

In another Finnish study including patients with endovascular and open surgical revascularisation, an association was observed between ulcer healing and angiosome targeted revascularisation only after adjustement for the number of affected angiosomes and CRP (Spillerova et al. 2017).

2.8.1.4 COLLATERALS

Interest has been growing towards the indirect revascularisation of an angiosome through collaterals (Varela et al. 2010, Alexandrescu et al. 2019, Acin et al. 2014, Zheng et al. 2016). Some studies show that the outcome is similar irrespective of whether the angiosome is revascularised by the source artery or the collaterals but that indirect revascularisation without collaterals has an inferior outcome.

In a study from Belgium, the ulcer healing rate within one year was 70% (79/113) in the group with direct angiosome-targeted revascularisation, 54% (15/28) in the group with collaterals to the ulcer angiosome, and 20% (7/35) in the group with indirect revascularisation. The mean ulcer healing times were 6.8±0.4 months, 7.9±0.6 months,

and 9.8±0.7 months, respectively. The estimated limb salvage at six months was better, 86%, in the group with direct angiosome-targeted revascularisation, compared to the 61% in the group with collaterals to angiosome and to the 58% in the group with indirect revascularisation. Notably, the mean follow-up time of the study was short (10.9 months, range 3–12.5), the number of patients in the two latter groups was quite small and the definition of collaterals was ambiguous. The revascularisation of 18 patients was not successful. (Alexandrescu e al. 2019)

In a Chinese study, 486 patients undergoing endovascular treatment for infrapopliteal CLTI and a tissue lesion were retrospectively divided into three groups: direct revascularisation of the angiosome, indirect revascularisation through collaterals and indirect revascularisation without collaterals based on postprocedural angiography. The direct revascularisation group and the revascularisation through collaterals group had similar unhealed ulcer and limb salvage rates, whereas the group without collaterals had a significantly higher rate of non-healed ulcers and a lower leg salvage rate. Diabetic patients without collaterals had an unhealed ulcer rate of 90% at one year, compared to 75% in non-diabetic patients. (Zheng et al. 2016.)

The 12-month ulcer healing rate was 55% among 92 diabetic patients with a combined 101 footulcers after an attempt at infrapopliteal endovascular revascularisation. The technical success rate was 86%. Indirect revascularisation with collaterals to the ulcer area (n=22) resulted in a 12-month ulcer healing rate of 68%, with no significant difference in comparison to the 66% ulcer healing rate after direct revascularisation (n = 46). On the contrary, after indirect revascularisation without collaterals, the healing rate was only 7%. In the group where no patent tibial arteries were achieved, the ulcer healing rate was 14%. (Acin et al. 2014.)

2.8.1.5 PEDAL ARCH

In a series including patients withn open surgical revascularisations, 66/141 patients with a tissue defect had no possibility of angiosome-targeted revascularisation. The quality of the pedal arch was associated with ulcer healing and leg salvage, whereas the revascularisation of the angiosome of the tissue defect was not. Amputation-free survival and graft patency were similar in all pedal arch groups. (Rashid et al. 2013.) Similarly, in an Italian study, open pedal arch was associated with improved wound healing rate, one-year leg salvage rate and one-year survival rate whereas direct revascularisation to angiosome had no significant association to outcome. (Troisi et al. 2017).

Higashimori et al. observed that the leg salvage was better in patients with open connections through the pedal arch after infrapopliteal endovascular treatment of CLTI, independent of which artery was recanalised and where the ulcer was located

(Higashimori et al. 2016). In contrast, Kret et al. found that, among 97 patients undergoing a combined 106 bypass operations for CLTI, the quality of the pedal arch was not associated with ulcer healing but that angiosome-targeted revascularisation was (Kret et al.2014).

2.8.1.6 HEEL ULCERS

Ischaemic heel ulcers are often regarded as having a poor outcome. Studies report varying results, but small superficial ulcers tend to heal well. IIschaemia, nephropathy, oedema, osteomyelitis and gangrene are associated with an unsuccessful outcome. (Örneholm et al 2017, Bosanquet et al. 2015, Dosluoglu et al. 2007). Indeed, in a study from a limb preservation clinic with 68% diabetic patients, hind foot lesions were associated with a failure to heal.s. (Vartanian et al. 2015.) Chipchase and colleagues studied the healing of 154 heel ulcers among 97 diabetic patients. Surprisingly, only 35% of the diabetic patients with heel ulcers had successful healing after revascularisation. In contrast, the healing rate was 84% among patients with palpable pulses. Cases with osteomyelitis were excluded, one fifth of the ulcers had an area smaller than 3 cm^2, and 86% of the ulcers were superficials. (Chipchase et al. 2005.)

However, severe ulcers may well heal with active treatment. A cohort study of 768 patients showed a 65% healing rate of heel ulcers. Paradoxically, however, in addition to nephropathy and oedema, vascular surgery was also associated with poor healing (Örneholm et al. 2015).In contrast, after bypass to the dorsal pedal artery, the outcome of heel lesions was comparable with forefoot lesions. The bypass was performed for 336 patients with forefoot lesions, 67 with heel lesions and 29 with both heel and forefoot lesions; 304 (90.5%) patients with forefoot lesions and 84 (86.5%) of the heel lesions healed. The above-knee (0.9% and 1.0%) and below-knee (8.9% and 8.3%) amputation rates were similar among the patients with forefoot and heel lesions, respectively. No difference was found in the wound healing rates of forefoot and heel lesions – 90.2% and 83.7%, respectively – irrespective of whether the pedal arch was complete (48%) or not. (Berceli et al. 1999) In another study, 71 legs with ulcers or gangrene of the heel and 237 legs with ulcers in other parts of the foot were revascularised either by vascular reconstruction or endovascular treatment and debridement, repeatedly if necessary. However, 11% of the patients with heel ulcers versus 3% with non-heel ulcers underwent primary amputation ($p < 0.001$). Leg salvage after revascularissation was similar in patients with heel ulcers and those with non-heel ulcers, whereas mortality was higher among patients with heel ulcers, 63% vs 43% ($p < 0.001$), respectively. Gangrene, dependence on dialysis treatment and low albumin levels were associated with major amputation in patients with heel ulcers and gangrene. Diabetes was present in 74% of the patients. (Dosluoglu et. al 2007.)

In severe tissue defects, the posterior part of the calcaneus can sometimes be removed and the defect closed primarily or after local treatment; for example, NPWT and STSG. A retrospective survey after partial calcanectomy in 42 patients (80% DM) showed no difference in amputation or patient ambulatory status irrespective of whether the resection was less or more than 50%. A major amputation was unavoidable in 28% of the patients, but the rate in relation to time or the rate of healing was not given. Approximately 45% of the patients had some vascular intervention. (Oliver et al. 2015.)

2.8.1.7 HEALING TIME

Median ulcer healing times vary substantially between studies, ranging from 2.5 months to up to 14 months, probably due to different patient selection. In specialised foot clinics, short healing times are probably explained by, in addition to specialised care, the small size of ulcers and the exclusion of hospitalised patients. In an English cohort of patients with diabetic foot ulcers of both neuropathic and ischaemic origin, the median ulcer healing time was 78 days (range 7–364 d). Seventy-eight percent of the ulcers were superficial, 61% had an area smaller than 1 cm^2, 48% were ischaemic and 41% infected. (Jeffcoate et al. 2006.) In another study, the healing of mostly superficial ulcers, only 10% UT 3D, took a mean of 165 days (Akturk et al. 2019). Yet, the average healing time was as short as 12 weeks in a limb preservation clinic where 44% of the ulcers were complex neuroischaemic ones (Vartanian et al. 2015).

After bypass surgery, median wound healing times were observed to be longer in 74 diabetic (213 days) than in 76 non-diabetic patients (159 days) (Söderström et.al. 2008). After 250 infrainguinal vascular reconstructions (66% DM), ischaemic pedal lesions healed in median of 198 days (Chung 2006). In connection with bypass to the dorsal pedal artery, the mean healing time of heel ulcers that closed was 200 (24–1,225) days (Chipchase et al. 2005). The mean time to complete healing was 139 days (13–16d) for 96 heel ulcers after a bypass to the ADP (91% DM) (Berceli 1999).

In one series, sssthe mean healing times after direct revascularisation, revascularisation through collaterals and indirect revascularisation were 6.8, 7.8 and 9.8 months, respectively (Alexandrescu et al. 2019). The healing times are associated with the tissue lesion and extensiveness of surgery. Among 701 patients with a plantar forefoot ulcer, the median healing time after inclusion was 17 (range 1–252) weeks, being 36 weeks after minor or major amputation (n=60), 21 weeks after debridement (n=173), and 13 weeks without major debridement (n=385). Eighty-three (12%) patients died with unhealed ulcers. (Örneholm et al. 2015.)

2.8.1.8 REULCERATION

The reulceration rate has ranged from 13% to 33% with follow-up periods varying between 8 months and 6 years (Faglia et al. 2009, Vartanian et al. 2015, Elgzyri et al. 2015, Iwase et al. 2018, Akturk et al. 2019). The ulcer recurrence rate at a limb preservation centre was as high as 45% during a median follow-up of 395 (80–635) days (Ramanan et al. 2017). In a British study consisting of a population with approximately 60 000 diabetic patients in a defined geographical area, the risk factors for the recurrence of first diabetic ulcer in a univariate model were age, type and treatment of diabetes, microvascular complications and location of ulcer. In a multivariate model, also including smoking status and depression classification, only microvascular complications were associated with recurrence. Remarkably, patients with severe ischaemia, dementia or rheumatoid arthritis and many more, were excluded from the study. (Winkley et al. 2007.)

2.8.1.9 ULCER-FREE TIME

Ulcer recurrence is frequent. Thus, the ulcer-free time provides additional outcome data compared to ulcer healing only. In one series, the ulcer healing rate over 12 months among 158 diabetic patients was 67% and the recurrence rate 31%. The mean ulcer-free time for healed ulcers was 212 days within 12 months and 130 days for all patients. Diabetes duration, CLTI, coronary artery disease, end stage renal disease (ESRD) and infection were independently associated with shorter ulcer-free time. (Akturk et. al 2019.)

2.8.2 LIMB SALVAGE

The limb salvage rate refers to the proportion of patients who have not had a major amputation (amputation above ankle level) during follow-up. As deaths do occur in this patient population, limb salvage is an estimate usually presented as a percentage of the initial population. The time interval from the evaluation of the ulcer to revascularisation has a significant influence on limb salvage (Sheahan et al. 2005, Elgzyri et al. 2013, Noronen et al. 2017). According to a systematic review including 19 studies, the 1-year median limb salvage rate after surgical revascularisation of ulcerated diabetic feet was 85% (IQR 80%–90%). After pedal bypass, the 1-year and 5-year median limb salvage rates were 86% (IQR of 85%–98%) and 78% (IQR 78%–82%), respectively. (Hinchliffe et al. 2016.) A meta-analysis of reconstructions with popliteal inflow (86% diabetic patients, 88% tissue loss) consisting of 31 studies from 1986–2004 showed a 5-year foot preservation rate of 78% of the patients. The 1- and 5-year limb salvage rates after popliteal to tibial grafts were 88% and 80 %, respectively, and after popliteal to pedal

bypass 88% and 78%, respectively. (Albers et al. 2006.) A systematic review of patients with ischaemic diabetic foot ulcers shows that, following endovascular treatment, the median 1-year and 3-year limb salvage rate was 78% (IQR 70.5–85.5) and 77% (IQR 63%–80%), respectively. The 5-year limb salvage was reported in two studies, being 56% and 77%, respectively (Hinchliffe et al. 2016).

Four recent meta-analyses that were already mentioned in the context of ulcer healing, report a better limb salvage rate after angiosome-targeted than after non-angiosome-targeted revascularisation. One focussed on endovascular treatment among diabetic patients, the other three on the infrapopliteal and any lower limb endovascular and open revascularisation (Chae et al. 2016, Bosanquet et al. 2014, Biancari and Juvonen 2014, Jongsma et al. 2017). In one of the meta-analyses, the pooled limb salvage in patients with direct revascularisation after any lower limb endovascular and open revascularisation swas 86% at one year and 85% at two years, whereas indirect revascularisation resulted in rates of 78% and 70%, respectively. More than 70% of the patients had diabetes (Biancari and Juvonen 2014).

The location of the ulcer was insignificant for limb salvage after bypass to the ADP. The 1- and 5-year limb salvage rates were 93.5% vs 94.2% and 89.4% vs 87.4% in patients with heel or forefoot ulcers, respectively (Berceli et al. 1999). After revascularisation, no significant difference seems to exist between diabetic and non-diabetic patients as regards long-term limb salvage (Table 19). The 5- and 10-year limb salvage rates reported after 352 inframalleolar bypasses for CLTI performed between 2002 and 2013 in Helsinki were 72.0% and 67.2%, respectively. The majority of the patients had diabetes (69%), and limb salvage was equal in patients with and without diabetes (p = .460). (Saarinen et al. 2016.) Accordingly, no significant difference between 643 diabetic and 667 nondiabetic patients was observed in the rates of limb salvage at 5 and 10 years (88% and 76% vs 91% and 83%; log-rank test, P = .12) after bypass with infrainguinal outflow. Eighty percent of diabetic patients and 67% of nondiabetic patients had a non-healing ulcer or gangrene. (Ballotta et al. 2014.)

Table 19. limb salvage after revascularisation.

Author, year	Number of patients (DM)	Open/ endovascular	Limb salvage	Special
Pomposelli et al. 2003	865 (92%)	open	5-year 78%, 10-year 58%	pedal bypass
Panneton et al. 2000	157 (100%)	open	5-year 78%	inframalleolar bypass, tissue defect 93%
Panneton et al. 2000	57 (0%)	open	5-year 78%	inframalleolar bypass, tissue defect 79%
Ballotta et al. 2014	643 (100%)	open	5-year 88%, 10-year 76%	infrainguinal outflow, 80% tissue defect
Ballotta et al. 2014	667 (0%)	open	5-year 91%, 10-year 83%	infrainguinal outflow, 67% tissue defect
Berceli et al. 1999	336	open	1-year 94.2%, 5-year 87.4%	pedal bypass, forefoot ulcer
Berceli et al. 1999	96	open	1-year 93.5%, 5-year 89.4%	pedal bypass, heel ulcer
Sheahan et al. 2005	670 (92%)	open	1-year 90%, 5-year 82%	all subsequent or previous minor amputation
Hughes et al. 2004	98 (84%)	open	1-year 75%,5-year 69%	plantar arteries/ lateral tarsal artery, 95% tissue defect
Azuma et al. 2012	228 (81%)	open	2-year 93%	100% ulcer or gangrene
Alexandrescu et al. 2009	176 limbs (100%)	endo	1-year 89%, 3-year 80%	100% ulcers
Acin et al. 2014	46 (100%)	endo	2-year 89%	100% ulcers, direct to angiosome
Acin et al. 2014	22 (100%)	endo	2-year 85%	100% ulcers, indirect with collaterals to angiosome
Acin et al. 2014	17 (100%)	endo	2-year 59%	100% ulcers, indirect without collaterals
Söderström et al. 2013	121 (100%)	endo	1-year 86%	infrapopliteal, direct to angiosome, 100% ulcer or gangrene
Söderström et al. 2013	129 (100%)	endo	1-year 77%	infrapopliteal, indirect to angiosome, 100% ulcer or gangrene

2.8.2.1 RISK FACTORS FOR MAJOR AMPUTATION

Many factors have been associated with poor limb salvage. Diabetes, in addition to the degree of ischaemia and infection, was associated with major amputation within one year of revascularisation among 139 patients (66% diabetic individuals) with a combined 158 ischaemic ulcers scored according to the WIfI classification s(Cull 2014).

In patients with a DFU an ulcer diameter of over 3 cm, associated osteomyelitis and ESRD predicted limb loss after revascularisation (Alexandrescu et al. 2009). The risk factors for major amputation in patients with a DFU were bony invasions, dialysis, gastrointestinal disorders, hind foot locations, low levels of haemoglobin and elevated fasting blood sugar levels (Namgoong et al. 2016).

A cohort of 2,511 consecutive patients from a multidisciplinary diabetic clinic were followed prospectively. Amputation in connection with neuro-ischaemic ulcers was related to comorbidity, peripheral vascular disease and the type of ulcer. Age, sex, duration of DM, neuropathy, deformity, duration of ulcer or site of ulcer were not related to the probability of amputation (Gershater et al. 2009) (Table 20).

In a multivariate analysis included in one study, any lower-extremity amputation (including minor amputations) due to an infected diabetic foot ulcer was associated with periwound oedema, foul smell, increased exudate and pus, ulcer depth, pretibial oedema, a body temperature of > 38°C, and high CRP. (Pickwell et al. 2015).

Table 20. Factors related to major amputation in connection with neuroischaemic/ ischaemic ulcers. Reproduced with permission from Gershater et al. 2009.

Factor	Odds ratio	95% CI	p-value
Duration of diabetes >23 years	1.88	1.15–3.50	0.011
Uraemia	2.43	1.33–4.45	0.004
Oedema	2.51	1.79–3.54	0.000
Foot deformity	1.69	1.08–2.63	0.021
Toe pressure < 30 mmHg	1.70	1.20–2.40	0.003
Intermittent claudication	1.88	1.25–2.82	0.002
Rest pain	2.06	1.45–2.98	0.000
Multiple ulcers	2.92	1.90–4.49	0.000
Non-compliant	2.15	1.26–3.66	0.005
Male sex	1.51	1.06–2.15	0.021

2.8.3 AMPUTATION FREE SURVIVAL

Whether the outcome of diabetic patients after bypass surgery is worse than that of nondiabetic patients is controversial and probably depends on the point of view. In a registry-based study from the US, CLTI was a more important predictor of low AFS than DM in patients with lower extremity ulcers. Patients with LEAD only were 8 years older than patients with LEAD and DM. (Humphries et al. 2016.) Furthermore, no significant difference between 643 diabetic and 667 nondiabetic patients with CLTI was observed in the rates of AFS at 5 and 10 years after infrainguinal vascular reconstruction by a single surgeon (45.5% and 27% vs 51% and 29%; log-rank test, P =.19) (Ballotta et al. 2014). However, population-based data achieved from a Swedish national register showed that, after lower extremity bypass for CLTI, AFS was lower in diabetic than in nondiabetic patients. The age-adjusted hazard ratio (HR) for death or ipsilateral major amputation was 1.55, and for ipsilateral major amputation 1.67 in diabetic patients. Diabetic patients were younger but had more severe tissue defects and more comorbidities. Type 1 and type 2 diabetes could not be analysed separately. (Malmstedt et al. 2008.)

2.8.4 SURVIVAL

Mortality among patients with DFU is high (Armstrong et al. 2020). The ten-year survival of diabetic patients under 65 years of age presenting with first foot ulcer was 85%, of patients aged 65-74 years the survival was 50% and of patients ovet 74 years it was 25% in a NHS area of the UK. In patients with new DFU combined with LEAD 5-year survival was 35%. (Paisey et al.2019) Three-year mortality in patients with diabetic foot ulcers was 26% in a Canadian register-based study (Hopkins et al. 2015). Five-year mortality in a cohort of 185 diabetic patients with new foot ulcers and ischaemia was 56%, whereas it was significantly lower, 45%, in patients with neuropathy. However, the only factor associated with mortality in the multivariate model was age. Accordingly, patients with ischaemic ulcers were older than patients with neuropathic ulcers. Five-year mortality was similar in patients with a new diabetic foot ulcer, either neuropathic or ischaemic, who underwent minor or major amputation and in patients who had ulcers but no amputation: 47% and 43%, respectively. (Moulik et al. 2003.)

One-year survival after revascularisation for DFU has been approximately 90% and five-year survival circa 50% (Faglia et al. 2009, Hinchliffe et al. 2016). A Swedish register-based study showed an increased risk of death (HR 1.49, 95% CI 1.30–1.71) among diabetic patients compared to non-diabetic patients after revascualrisation fot CLTI (Malmstedt et al. 2009). In contrast, no significant difference between diabetic and nondiabetic patients was observed in the rates of survival at 5 and 10 years after vascular reconstruction for CLTI (51% and 34% vs 57% and 38%; log-rank test, P = .41) (Ballotta et al. 2014). After bypass surgery for patients with Fontaine IV foot lesions (55% DM), the survival rates at one, three and five years were 71%, 53% and 38%, respectively

(Söderström et al. 2010). The five- and ten-year survival rates after pedal bypass for limb salvage (92% DM) were 49% and 24%, respectively (Pomposelli et al. 2003).

2.8.5 CLINICAL/FUNCTIONAL OUTCOME

Taylor et al. studied the clinical outcome of revascularisation in patients with ischaemic tissue loss (68% DM) (Taylor et al. 2009). Four criteria needed to be fulfilled in clinically successful revascularisation: the treated segment should stay open until wound healing, ambulation at 1 year, at least 1-year limb salvage, and 6-month survival. The failure rate among diabetic patients was 64%. Among diabetic patients with impaired preoperative ambulation, 74% failed to fulfil the criteria. Of diabetic patients with impaired ambulation and ESRD, the failure rate was 82%. For diabetic patients with impaired ambulation and gangrene, the failure rate was 85% and for diabetic patients with ESRD 58%. Among diabetic patients with ESRD, impaired ambulation, gangrene and a prior revascularisation, the failure rate was 93%. (Taylor et al. 2009.) Iida et al. studied the outcome of 662 patients with CLTI who needed assistance in daily living and/or had impaired cognitive function. Of these patients, 562 were in the revascularisation group and 100 in the non-revascularisation group. Functional ability after one year was similar to the baseline functional ability, but the quality of life quality had improved in the revascularisation group. (Iida et al. 2017.)

ESRD is significantly associated with poor outcome. Jones et al. studied the outcome one year after revascularisation. Only 40% of patients with ESRD and tissue loss (85% DM) remained alive for at least 6 months, had the bypass open until the healing of the tissue lesion, remained ambulatory for at least six months and had their limb intact for one year after surgical revascularisation (Jones et al. 2007). In another study, 70 patients with a technically successful vascular reconstruction for limb-threatening ischaemia (open in follow-up) had a decreased walking capacity and were less able to manage household tasks and shopping, prepare meals, bathe, drive a car and participate social activities when compared to an age- and sex-matched control group . No significant difference was observed in dressing and going to the toilet. Despite these functional impairments, patients with vascular reconstructions had a similar sense of wellbeing and a similar amount of health complaints to the control group. (Seabrook et al. 1999.)

In order to study ideal recovery from infra-inguinal open revascularisation, data on the functional status, wound healing time, the need for repeat operations, recurrent ischaemia, postoperative complications, mortality, graft patency and leg salvage were analysed among 112 patients (53% DM). Fourteen percent of the cohort reached the ideal outcome with prompt healing, long-term disease control and the maintenance of functional capacity without postoperative complications, reoperations or relapses. (Nicoloff et al. 1998)

Of ambulatory, nursing home residents 63% remained nonambulatory or died within one-year after open surgical or endovascular revascularisation. Age over 80 years, cognitive impairment, congestive heart failure, renal failure, emergent surgery, non-ambulatory status before surgery, and a decline in daily activities before surgery were associated with death or nonambulatory status after revascularisation. (Oresanya et al. 2015.)

2.8.6 OUTCOME OF FREE TISSUE TRANSFER

2.7.6.1 GENERAL POSTOPERATIVE COMPLICATIONS

The risk of complications after FTT is high, as the overall 30-day complication rate has been 30%–50% (Moran et al. 2002, Randon et al. 2010, Fitzgerald O'Connor et al. 2011). The most common fatal complication has often been congestive heart failure. In Belgium, in addition to three fatal congestive heart failures in 76 patients, three patients suffered strokes with a good recovery (Randon et al. 2009). Congestive heart failure was also observed in 6 out of 76 patients in Rochester, 4 with a fatal outcome. A further two non-fatal AMs (acute myocardial infarctions) were encountered. The one of these two patients developed intestinal ischaemia, which was operated on successfully. (Moran et al. 2002.) In an earlier series from Helsinki University Hospital, 3 respiratory, 2 cardiac and renal complications, 1 cerebrovascular complication, and 1 multiorgan failure occurred. Furthermore, 2 cases of sepsis were encountered. The one of these was due to sacral decubitus. (Tukiainen et al. 2000.) The 30-day postoperative mortality was 3%–5% in a large meta-analysis (Fitzgerald O'Connor et al. 2011). The two largest series report 30-day postoperative mortality rates of 5% and 3.8%, respectively (Moran et al. 2002, Randon et al. 2009), and mortality was lower among diabetic patients, only 2%. (Randon et al. 2010). Diabetes alone and combined with ESRD were associated with mortality (Illig et al. 2001). In the earlier series from Helsinki, one patient with open sacral decubitus died of sepsis on the 40th postoperative day, accounting for a 3.4% mortality (Tukiainen et al. 2000).

2.8.6.2 POSTOPERATIVE FLAP AND DONOR SITE COMPLICATIONS

Minor complications are seen in 30% of the patients and include haematoma, infection and flap edge necrosis (Fitzgerald O'Connor et al. 2011, Moran et al. 2002, Randon et al. 2010, Tukiainen et al. 2000). Reinterventions are frequently necessary after FTT and include thrombectomies, reanastomosis of arteries or veins, new free flaps, skin grafts and amputations. (Table 21) The postoperative major amputation rate was 6% in two large studies (Randon et al. 2009, Moran et al.2002). Flap failure often leads to major amputation, while this end result is not as frequent with vascular graft thrombosis. The

reported total flap failure rates are 10%–25%. In a large series (433 patients), the overall failure rate was 10%; for patients who had free perforator flap (n=152), the rate was 15% and for patients who had LEAD (n=102) 25%. DM, LEAD, chronic ulcer, nephropathy, location in the foot and CHD were risk factors for an unsuccessful flap, whereas trauma was associated with better success in univariate analysis (Koh et al. 2018). Among 231 FTTs due to various reasons, the leading cause being trauma, diabetes was a risk factor for flap failure in multivariate analysis (Cho et al. 2016).

Donor site problems are flap specific. The ALT-flap typically has a low frequency of complications (Randon et al 2009, Ren et al. 2015) In the LD flap donor site, a seroma or wound healing problems were observed in 5.3% of patients (Kim et al 2015). The shoulder extension strength diminished permanently but the subjective morbidity was low according to a study focusing on the latissimus dorsi muscle donor site problems (Salmi et al. 1995). In one meta-analysis some decrease in the strength and mobility of the shoulder region as determined by means of objective measurements and to patient questionnaires, as well as impairment of working ability and discomfort were observed (Lee et al. 2015). The rectus abdominis flap donor site complications include donor site healing problems 18%, mesh-problems and further, the abdominal wall laxity and hernias (Mirzabeigi et al. 2014, Randon et al. 2009). In one study, an unhealed donor site wound at six months was observed in 18 % of patients. (Mirzabeigi et al. 2014) In another study, an abdominal bulge and hernias were observed among 10% of patients (Sailon et al. 2009). Delayed healing and a partial loss of skin graft easily result in a tendon adhesion and furthermore, an impairment in hand strength and range of movement after raising of the radial forearm flap (Suominen et al. 1996). These problems are encountered in up to 10% of patients. In one study, dysesthesia was observed in half of the patients, but it usually resolved later (Lutz et al 1999). However, suprafascial elevation and a sheet skin graft may diminish the donor site problems of radial forearm flaps. (Chau et al. 2009, Lutz et al 1999)

Table 21. Postoperative outcome after FTT

Author, year	N	flap	revasc	Cl-D III *a*	partial flap loss *b*	total flap loss *c*	bypass thromb	major amp	death
McCarthy 1999 30-d	21	LD 5, omentum 5, RA 5, gracilis 2, RF 3, scapular 1	21	7	2	3	0	3	0
Tukiainen 2000 30-d	29	LD 20, 7 RA, RF 1, TFL 1, gracilis 1	29	10	5	4	2	1	0
Moran 2002	75	RA 35, LD 15, RF 24, scapular 3, omentum 2	61(81%)	-	7	6	9	5	4
Randon 2010	55	RA 44, LD 5, ALT 3, serratus anterior, lateral arm	55	17	?	5	6	5	1
Gooden 1997	26	RA 9, RF 8, LD 7, scapular 3	17 (65%)	9	4	2	2	2	2
Huang 2014	24	LD and RA	24 (endo)	12	3	0	-	0	1
Oh 2012	121	ALT 90, SCIP 20, AMT 5, UMT 3	9+endo5 (11,5%)	10	14	10	-	-	-
Lee 2014	33	ALT 19, TAP 9, gracilis 5	33 open or endo	8	-	10	3 *d*	-	-

revasc (revascularisation), Cl-D (Clavien-Dindo), partial fl (partial flap loss), bypass thromb (bypass graft thrombosis) LD (latissimus dorsi), RA (rectus abdominis), RF (radial forearm), TFL (tensor fasciae latae), ALT (antero-lateral thigh), SCIP (superficial circumflex iliac artery perforator) AMT (anteromedial thigh), UMT (upper medial thigh), TAP (thoracodorsal artery perforator)
a no major amputation *b* included in Clavien-Dindo classification *c* not included in Clavien-dindo *d* (included in flap loss)

2.8.6.3 LONG-TERM OUTCOME

The complete healing of all wounds in an ischaemic foot takes an average of 4 months (range 1–8) after FTT (McCarthy et al. 1999). The reported one-year limb salvage rate among diabetic patients after FTT has been 70%–96% (Huang et al. 2014, Moran et al.

2002, Randon et al. 2010). The average limb salvage in a meta-analysis on FTT in diabetic feet was 83.4% over an average of 28 months (1–68) of follow-up (Fitzgerald O'Connor et al. 2011). Amputations mostly occur during the first two years after the operation. In an all-diabetic population, the 5-year limb salvage rate was 64% (Randon et al. 2010). LEAD and PTA were correlated with flap loss (OR 17.6 and 10.2), in addition to immunosuppressive medication related to kidney transplantation (OR 4.9) (Oh et al. 2013). Atherosclerotic calcifications ($p = 0.002$) and elevated serum creatinine levels ($p = 0.04$) were associated with partial or total flap loss (Lee et al. 2014). Renal insufficiency has also been identified as a risk factor for limb loss after FTT and vascular reconstruction, with an HR of 5.6 (95% CI 1.4–22.5) (Randon et al. 2010). However, location (foot vs leg), weight bearing flap, hypertension, previous acute myocardial infarciotn (AMI), osteomyelitis, inflow vessel, the timing of vascular reconstruction and flap type, in turn, have not been established as risk factors for FTT failure (Moran et al. 2002).

3 AIMS OF THE PRESENT STUDY

1) To evaluate the incidence and risk factors of lower extremity arterial disease in type 2 diabetic patients (Study I).

2) To assess the long-term limb salvage rates and risk factors of amputation after combined vascular reconstruction and microvascular free-flap transfer in patients with critically ischaemic large tissue defects (Study II).

3) To analyse the impact of the severity of LEAD and other risk factors on the long-term outcome after FTT for large diabetic foot lesions (Study III).

4) To prospectively evaluate the long-term survival, limb salvage, ulcer healing and reulceration rate in nonselective consecutive patients with an ischaemic foot ulcer visiting a university hospital vascular surgery unit, and to assess the risk factors for amputation (Study IV).

4 MATERIAL AND METHODS

The thesis includes three cohorts of patients. One was a cohort of 130 type 2 diabetic patients, the second was a cohort of 96 consecutive patients who underwent free flap transfer between in order to treat large tissue defects of the diabetic or ischemic foot, and the third was a cohort of 95 consecutive patients who were referred for vascular surgical consultation and admitted to the ward for specific investigations. Two overlapping subcohorts were formed out of 96 patients who had undergone FTT: a cohort of 63 patients with diabetes and a cohort of 79 patients who underwent combined FTT and vascular reconstruction. Included in both cohorts were 51 patients with DFU who underwent combined FTT and revascularisation.

Table 22. Demographics of Studies I-IV

	Study 1	Study 2	Study 3	Study 4
Number of patients	130	79	63	95
Age, years	58±6 (42-69)	61±12	56 (IQR21)	71±12 (r40-92)
Male	51%	65%	70%	55%
Ever smoking	53%	28%	19%	62%
Type 1diabetes	0	26%	38%	9,5%
Type 2 diabetes	100%	47%	62%	46%
Coronary artery disease	13% (AMI+ECG)	35%	32%	54% (n=91)
Cerebrovascular disease	2,3% (n=129)	7%	11%	26% (n=91) *a*
Renal insufficiency	0	27%		23%
Uraemia	0		3%	7%
Renal transplantation	0	9%	13%	4%
ASA 4	0	25%	22%	
Revascularisation	2,3%	100%	84%	75%

a (inf tai EA) AMI acute myocardial infarction, ECG electrocardiogram, ASA American Society for Anesthesiologists, IQR = interquartile range.

4.1 STUDY I

4.1.1 PATIENTS AND STUDY DESIGN

In order to conduct a prospective cohort study, 130 type 2 diabetic patients, arbitrarily selected from the register of the Helsinki Diabetes Association, were examined at baseline in 1983–1985 and at follow-up in 1992–1993, an average of 11 years later (Table 22). Ninety-three patients were available for the follow-up study.

4.1.2 OUTCOME MEASURES

Study I focused on the risk factors of the presence of LEAD at baseline and on the development of new LEAD during follow-up. The primary endpoint was LEAD based on the ankle-brachial index, and if it exceeded 1.15, on toe pressure measurement in the vascular laboratory. Secondary endpoint data on deaths was obtained from the Digital and Population Data Services Agency. Causes of death were ascertained from medical records. Risk factor assessment was accomplished at baseline. Blood tests for HBA1c percentage, c-peptide, cholesterol and triglyceride concentrations were analysed at baseline. Urine albumin excretion rate (UAER) was calculated from 24-hour or overnight urine collection. EKG was taken and analysed according to the Minnesota coding. A review of medical history was ascertained from medical records.

4.1.3 STATISTICAL ANALYSIS

Categorical data were analysed with Fischer's two-tailed test and continuous data with the Mann-Whitney U test. For the identification of risk factors, Cox backward stepwise logistic regression analysis was applied. A significance level of $p < .05$ was used.

4.2 STUDY II

4.2.1 PATIENTS AND STUDY DESIGN

All 79 consecutive patients in Helsinki University Hospital who underwent FTT and vascular reconstruction for ischaemic foot defects from 1989 to 2003 were included in the retrospective cohort study (Figure 4. The follow-up data until the end of 2005 were retrieved from medical records, and, if necessary, via telephone calls to patients.

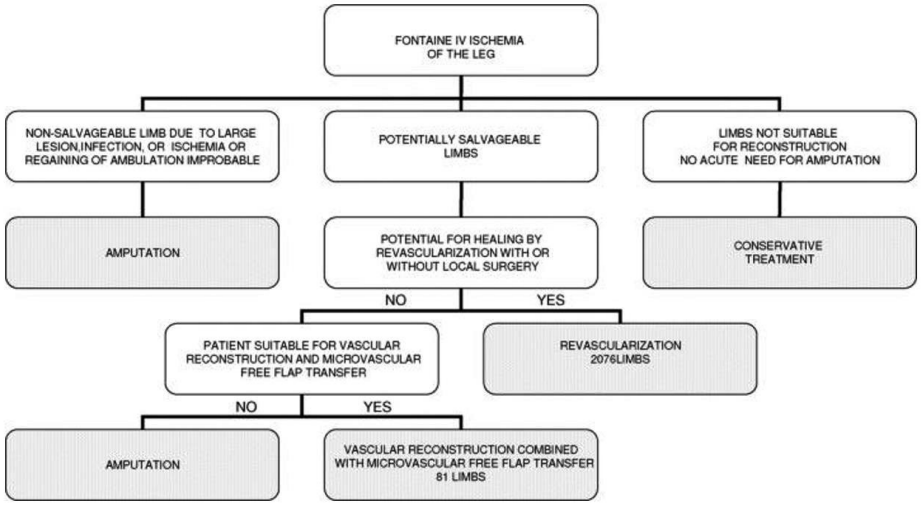

Figure 4. Decision tree for the treatment of ischaemic lower extremity ulcers in Helsinki University Hospital. Reproduced with permission from Tukiainen et al. 2003.

4.2.2 OUTCOME MEASURES

The primary endpoint was amputation, and the secondary endpoints were amputation-free survival and death. Amputation and operation data were available form medical records. Amputations were confirmed from HILMO (Care register for health care) and deaths from the Digital and Population Data Services Agency. Demographics, medical history, the characteristics of the ulcers, noninvasive vascular measurements, angiographic findings and operation details were based on medical records. (Tables 22 and 23.)

Table 23. Location of tissue defects

Location	Number of defects
Forefoot	30
Dorsum of the foot	8
Heel	18
Mid-foot plantar	3
Tarsal	5
Achilles tendon region	3
Lower leg	14

4.2.3 STATISTICAL ANALYSIS

Categorical data were analysed with Pearson's X^2 test, and log-rank test was used for the comparison of 2 groups. Survival and amputation data were compared with Kaplan-Meier analysis. Cox backward stepwise logistic regression analysis was applied for the identification of factors influencing survival and major amputations. A p-value of $< .05$ was considered statistically significant.

4.3 STUDY III

4.3.1 PATIENTS AND STUDY DESIGN

All 63 consecutive diabetic patients whose tissue defect of the foot due to chronic ulceration or gangrene was covered with FTT in Helsinki University Hospital during 1991–2003 were included. Three groups with different strategies required to overcome ischaemia were observed (Figure 5). Patients in group NA (native artery) had patent native arteries and no need for vascular reconstruction. Patients in group C (correctable ischaemia) underwent vascular reconstruction to overcome ischaemia. Patients in group U (uncorrectable ischaemia) were lacking a recipient artery in the ulcer area, making vascular reconstruction to overcome ischaemia impossible. The follow-up lasted until the end of year 2009 or to the death of the patient.

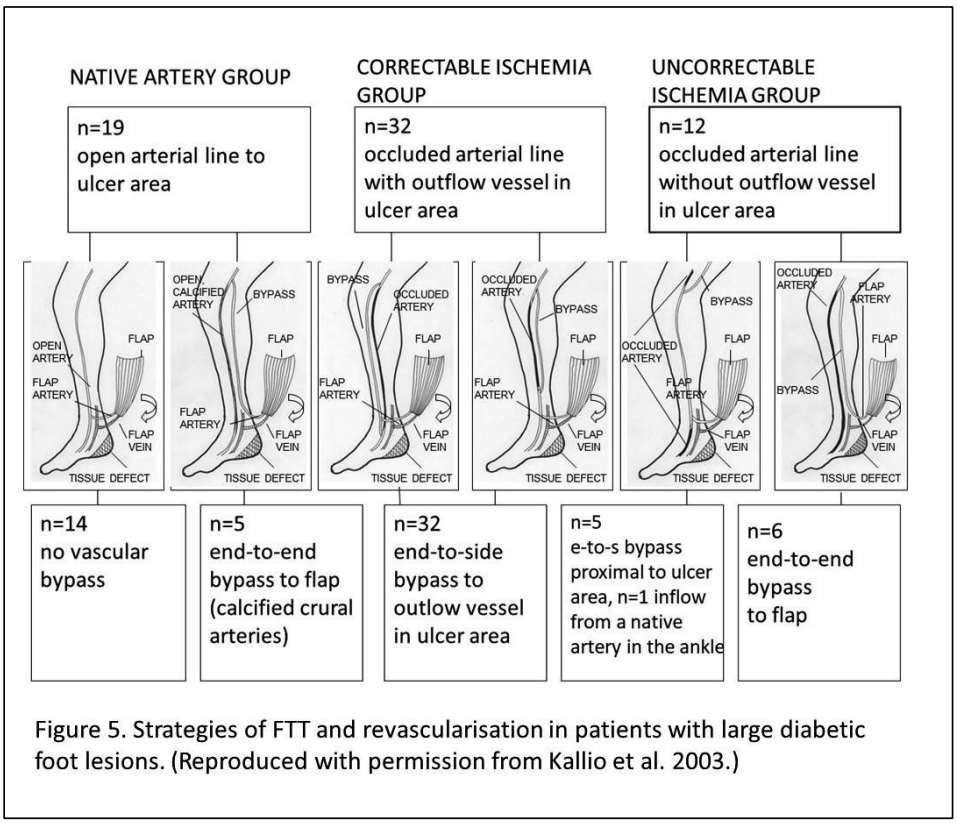

Figure 5. Strategies of FTT and revascularisation in patients with large diabetic foot lesions. (Reproduced with permission from Kallio et al. 2003.)

4.3.2 OUTCOME MEASURES

The primary endpoint was a major amputation and secondary endpoints were ulcer healing, ulcer healing time, amputation free survival and death. The ulcer was considered healed if it persisted fully epithelised at least six months after healing.

The pre- and perioperative baseline data, demographics, the medical history, characteristics of the ulcers, the noninvasive vascular measurements, angiographic findings and operation details were retrieved from medical records and partly collected prospectively. The follow-up data was retrieved from hospital medical records as well as from the primary care centres and home nursing services.

4.3.3 STATISTICAL ANALYSIS

Baseline data were compared between the groups using the chi-squared Pearson's or , Fischer's exact test or the Mann-Whitney U test, as appropriate. Survival was studied by means of Kaplan-Meyer analysis. The estimated median survival was given with a 95% CI. Risk factors for endpoints were tested with the log-rank test. A p-value of $< .05$ was considered statistically significant.

4.4 STUDY IV

4.4.1 PATIENTS AND STUDY DESIGN

In 1999, 99 consecutive patients with ischaemic ulcers admitted to the wards for angiography by appointment or as emergency cases were interviewed, and the ulcers were examined. In 1999, angiography was the primary diagnostic method following vascular laboratory measurements and required an inpatient admission. Follow-up data were retrieved ten years later from patient records and by means of telephone interviews when necessary. Baseline examinations revealed 4 non-ischaemic ulcers, which were excluded from the study, leaving 95 patients (Figure 6).

4.4.2 OUTCOME MEASURES

Primary endpoint was amputation and secondary endpoints were postoperative mortality and amputations above the ankle level, as well as limb salvage, survival, amputation-free survival, ulcer healing, mean ulcer healing time and mobility. An ulcer

was considered healed if it was still fully epithelised after six months. Smoking, ulcer duration, mechanism of ulceration and mobility, as well as the diameter, depth, signs of infection, location and the number of ulcers were recorded. The medical history was ascertained from the medical records. The feeding arteries of angiosomes could be ascertained for 91 patients from angiographic findings and operation data. Feeding arteries and angiosomes were defined as follows: the ADP and distal ATP for the toes; the distal ATP for the plantar surface; the distal ATP and fibularis for the heel; the ADP for the dorsal surface of the foot; and all three arteries of the leg for the ankle and leg.

4.4.3 STATISTICAL ANALYSIS

In Study IV, factors associated with amputation, death and ulcer healing were analysed. Pearson's chi-squared and Mann-Whitney U tests were used to study univariate associations. Independent associations with endpoints were analysed with a COX logistic regression model. The Kaplan-Meier test was used for survival analysis.

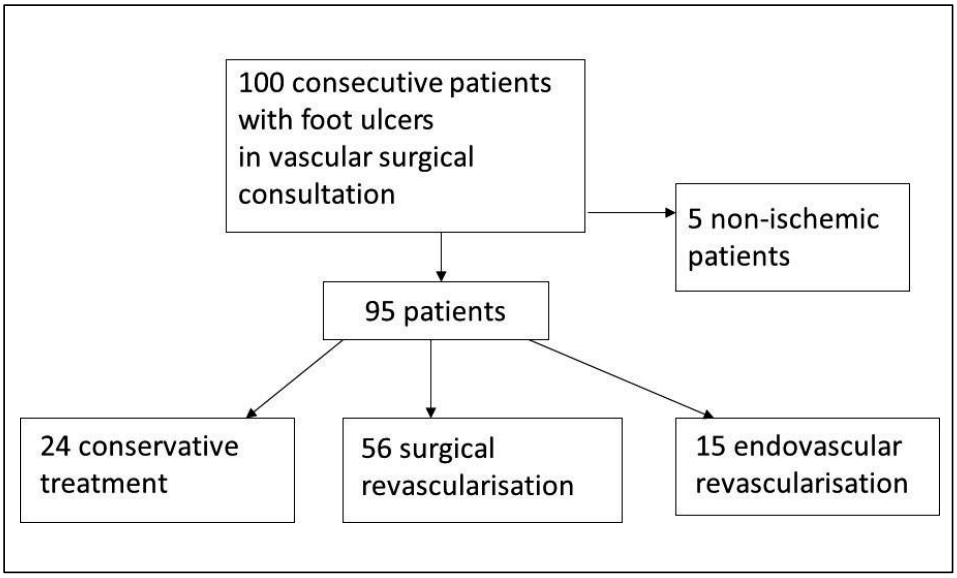

Figure 6. Patients and treatments at baseline in Study IV

5 RESULTS

5.1 LEAD IN TYPE II DIABETIC PATIENTS (STUDY I)

5.1.1 INCIDENCE

At baseline, 16% of type 2 diabetic patients (mean age 58 years) had LEAD. During a mean 11-year follow-up, 24% of the patients developed new LEAD (Figure 7).

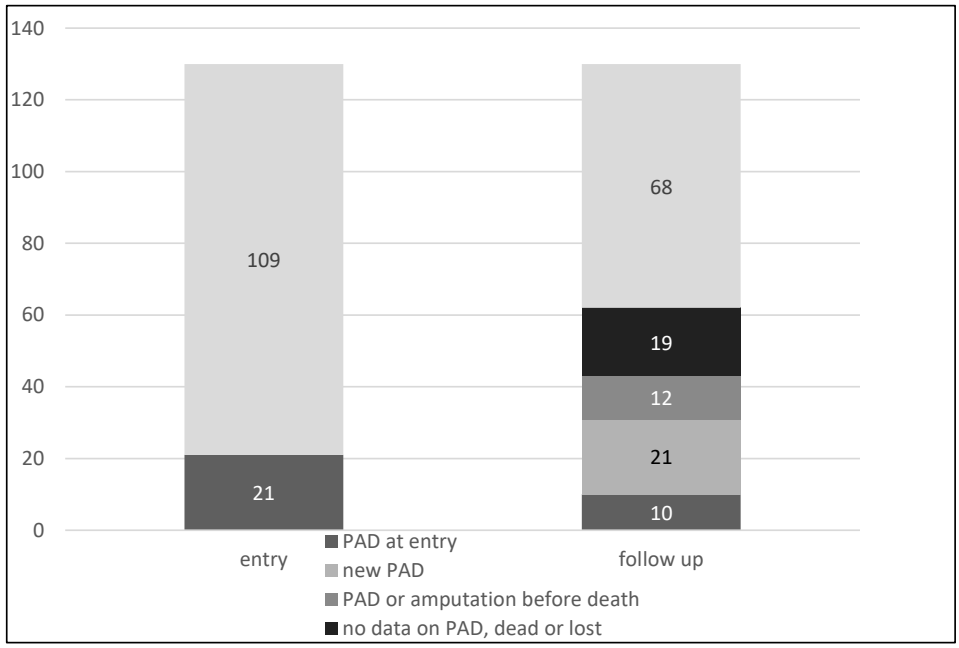

Figure 7. Patients in Study 1. PAD peripheral arterial disease. Reproduced with permission from Kallio et al. 2003.

5.1.2 RISK FACTORS

At the baseline, patients with LEAD were older, had a longer duration of diabetes, and were more often microalbuminuric than patients without LEAD (Table 24). In multivariate logistic regression analysis, LEAD was associated with age, the duration of diabetes, smoking and urinary albumin excretion rate (Table 25).

Table 24. Characteristics of the patients at baseline

	LEAD, 21 patients	no LEAD, 109 patients	p
Age (years)	61±0.8	57±0.6	0.01
Sex (% male)	57	50	
History of smoking (%)	71	50	
BMI (kg/m^2)	27±0.5	27±0.4	
Insulin treatment (%)	18	22	
Duration of diabetes (years)	12±1.0	9±0.4	0.01
HbA_1 (%)	10.6±0.4	9.9±0.2	
C-peptide (nmol/l)	0.48±0.06	0.47±0.03	
Systolic BP (mmHg)	156±7	153±2	
Diastolic BP (mmHg)	87±3	88±1	
Hypertension (%)	67	51	
Total cholesterol (mmol/l)*	6.5±0.3	6.3±0.1	
LDL cholesterol (mmol/l)*	4.4±0.3	4.3±0.1	
HDL cholesterol (mmol/l)*	1.3±0.05	1.4±0.04	
Triglycerides (mmol/l)*	2.8±0.5	2.3±0.2	
UAER (mg/24h)	61±19	12±2	0.0003
Microalbuminuria (%)**	52	11	<0.0001
ECG changes (%)	5	10	
History of MI (%)	1	8	
History of stroke (%)	2	1	

LEAD lower extremity arterial disease; BMI, body mass index; BP, blood pressure; UAER, urine albumin excretion rate; ECG, electrocardiogram; MI, myocardial infarction. HDL high density lipoprotein. Data are means ± SE or percentage. LEAD/no LEAD n= *22/104, **21/103.

Table 25. Factors associated with LEAD at baseline in multivariate analysis.

	Log likelihood ratio	Odds ratio (95%CI)
Age	p=0.03	1.15 (1.00–1.32)
Smoking	p=0.04	3.69 (0.98–13.84)
Duration of diabetes	p=0.05	1.13 (1.00–1.27)
UAER	p=0.002	1.02 (1.00–1.04)

UAER urine albumin excretion rate

The patients who developed new LEAD had higher lipid levels than patients who remained free of LEAD (Table 26). In multivariate logistic regression, age, high LDL cholesterol and low HDL cholesterol were associated with the development of new LEAD (Table 27).

Table 26. LEAD at follow-up: baseline characteristics of the 89 patients with no LEAD at baseline who participated in the follow-up study

	new LEAD (21 patients)	no LEAD (68 patients)	p
Age (years)	58.6±1.0	56.6±0.7	
Sex (% male)	38	49	
Smoking history (%)	57	44	
BMI (kg/m$^{2)}$	27±1	27±1	
Systolic BP (mmHg)	158±5	153±3	
Diastolic BP (mmHg)	88±1	88±2	
Hypertension (%)	48	52	
Insulin treatment (%)	14	24	
Diabetes duration (years)	9.9±0.6	8.5±0.6	
HbA_1 (%)	10.3±0.5	9.6±0.2	
C-peptide (mmol/l)	0.49±0.05	0.44±0.05	
Total cholesterol (mmol/l)	7.2±0.4	6.1±0.2	0.002
LDL cholesterol (mmol/l)	4.8±0.3	4.1±0.1	0.03
HDL cholesterol (mmol/l)	1.3±0.1	1.5±0.1	0.04
Triglycerides (mmol/l)	3.5±0.6	1.8±0.2	
UAER (mg/24h)	10±3	10±3	
Microalbuminuria (%)	10	7	

BMI body mass index; BP blood pressure; LDL low density lipoprotein; HDL high density lipoprotein; UAER urine albumin excretion rate; LEAD lower extremity arterial disease

Table 27. Factors associated with development of new LEAD in 89 patients free of LEAD at baseline

	p for log likelihood ratio	Odds ratio (95%CI)
Age	0.002	1.25 (1.06–1.48)
LDL cholesterol	0.002	2.97 (1.33–6.66)
HDL cholesterol	0.0003	0.009 (0.0003–0.23)
Follow-up time	0.008	1.62 (1.09-2.41)

5.1.3 LONG-TERM OUTCOME

During the follow-up, 29 patients (22%) died, 21 of cardiovascular causes. Mortality in patients with LEAD was high compared to patients without LEAD: 58% vs 16% ($p < 0.001$). An ABI of < 0.9 was strongly predictive of death in patients with no other sign of cardiovascular disease at baseline ($p < 0.001$).

5.2 EFFECT OF REVASCULARISATION ON THE LONG-TERM OUTCOME OF DIABETIC PATIENTS WITH ISCHAEMIC ULCERS (STUDY IV)

5.2.1 CHARACTERISATION OF PATIENTS AND ULCERS REFERRED FOR VASCULAR CONSULTATION

The cohort of patients with ischaemic ulcers was heterogeneous. Revascularisation was performed on 75% of the patients, whereas 25% received conservative treatment (Figure 6). The patient characteristics are presented in Table 28 and ulcer characteristics in Table 29. Revascularisation was performed for equally sized groups of type 2 diabetic patients and nondiabetic patients. In addition, a small group of seven patients with type I DM underwent revascularisation. Significant differences existed in cardiovascular and renal morbidity, as well as age and ulcer characteristics between the patient groups. Heel ulcers were common in patients with type 1 diabetes and deep ulcers and infection in patients remaining without revascularisation.

Table 28. Patient characteristics in Study IV

Variable	Revasc DM1 n=7	Revasc DM2 n=33	Revasc noDM n=31	NoRevasc n=24	sig.
male sex	4 (57)	22 (67)	13 (42)	13 (54)	b
age	45 (40–55)	74 (48–88)	76 (60–89)	73 (44–92)	a,d,e
no DM	0	0	31	11	
DM 2	0	33	0	11	
uraemia	3 (43)	2 (6)	0	2 (8)	a,d,e
renal transplantation	4 (57)	0	0	0	a,d,e
CVD	1 (14)	9 (27)	3 (10)	12 (50)	b,c
history of AMI	4 (57)	17 (52)	4 (13)	6 (25)	b,e
coronary bypass	4 (57)	7 (21)	2 (7)	6 (25)	a,c,e
body mass index	23 (18–29)	26 (17–40)	23 (18–34)	21 (15–51)	b
ever smoking	4 (57)	24 (73)	21 (70)	10 (42)	f
current smoking	2 (29)	3 (9)	12 (40)	5 (21)	b,c
contralat. major LEA	2 (29)	4 (12)	2 (7)	4 (17)	
C-reactive protein	13 (4–165)	20 (4–159)	13 (4–114)	60 (4–308)	c,f
leukocytes	11 (3.8–12.4)	8.2 (4.8–11.8)	7.3(3.6–13.9)	8.5 (4–24)	
creatinine	115 (64–999)	110 (67–596)	82 (57–140)n	115 (58–408)	b,c
GFR	57 (8–132)	54 (14–88)	52 (33–108)	42 (16–99)	
toe pressure	21 (0–39) n=6	19 (0–82) n=30	25 (0–63) n=28	0 (0–54) n=18	
ankle brachial index	0.69 (0.39–2) n=5	0.52(0.2–1.95) n=31	0.42 (0–1.67) n=29	0.53 (0.2–1.82) n=21	
living at home	6 (86)	27 (82)	26 (84)	17 (71)	
walking>100m*	3 (43)	6 (18)	5 (16)	0	d,f

a: significant difference between revasc DM 1 and revasc DM2
b: significant difference between revasc DM 2 and Revasc noDM
c: significant difference between Revasc noDM and Norevasc
d: significant difference between Norevasc and Revasc DM1
e: a significant difference between Revasc DM1 and Revasc noDM
f: a significant difference between Norevasc and Revasc DM2

Table 28: LEA lower extremity amputation; CVD cerebrovascular disease; AMI acute myocardial infarction; GFR glomerular filtration rate; Revasc revascularisation; sig. significance; * without aid

Table 29. Ulcer characteristics

Variable	Revasc DM1 n=7	Revasc DM2 n=33	Revasc noDM n=31	NoRevasc n=24	sig
ulcer in toes	4 (57)	20 (61)	10 (32)	17 (71)	b,c
ulcer in heel	3 (43)	7 (21)	3 (10)	4 (17)	a
ulcer in leg	0	3 (9)	8 (26)	1 (4)	c
ulcer in ankle	0	0	6	0	
ulcer dorsally	0	1	3	1	
plantar ulcer	0	2	1	0	
UT 3	4 (57)	14 (42)	4 (13)	17 (71)	b,c,e,
UT D	3 (43)	16 (49)	17 (55)	18 (75)	e
UT 3D	3 (43)	10 (30)	4 (13)	15 (63)	c,e
number of ulcers	1 (1–3)	1 (1–5)	1 (1–7)	2 (1–6)	
ulcer diameter, mm	26 (5–100)	24 (0.5–163)	29 (2–129)	17 (1–82)	

a: significant difference between revasc DM 1 and revasc DM2
b: significant difference between revasc DM 2 and Revasc noDM
c: significant difference between Revasc noDM and Norevasc
d: significant difference between Norevasc and Revasc DM1
e: significant difference between Revasc DM1 and Revasc noDM
f: significant difference between Norevasc and Revasc DM2
Revasc revascularisation; UT University of Texas classification

5.2.2 OUTCOME

Twenty-eight patients underwent a major amputation, and 83 patients died during the follow-up. Seven patients died within 30 days. Two patients had non-salvageable legs needing immediate amputation. Amputations were rare after one year. The leg salvage rate following revascularisation was similar in type 2 diabetic and nondiabetic patients: 106 (95% CI 90–123) months and 112 (95% CI 97–127) months, respectively (p = 0.55). One-, five-, and ten-year amputation free survival rates in the whole cohort were 59%, 31% and 11%, respectively (Figure 8). Events during the 10-year follow-up in each group are presented in Figure 9.

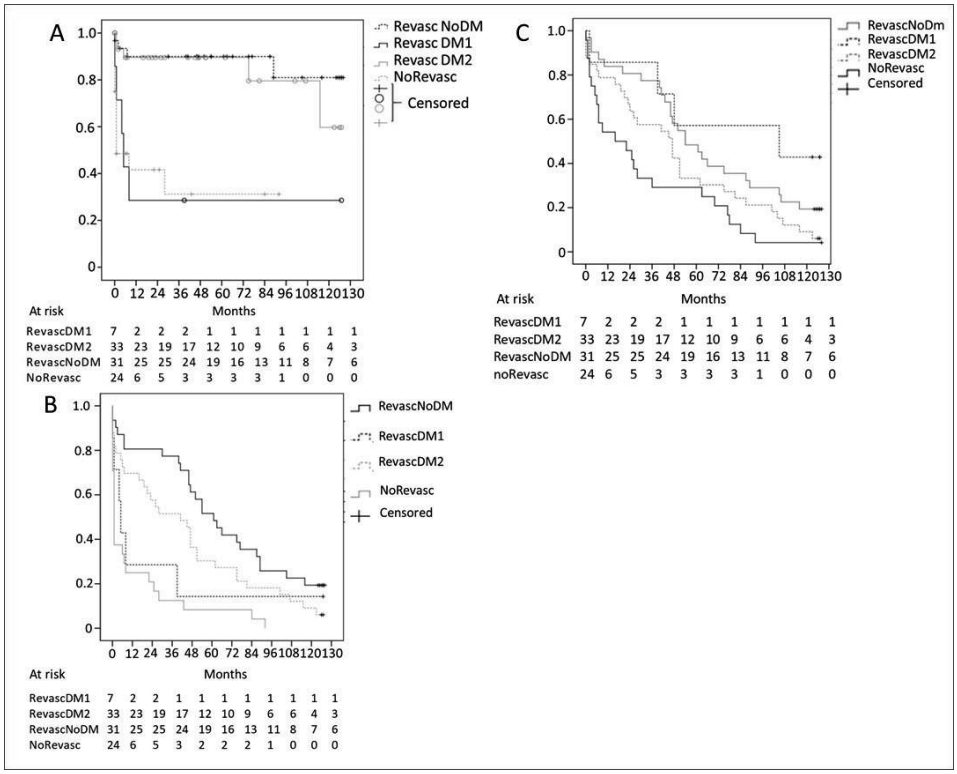

Figure 8. A) Leg salvage, B) survival, C) amputation-free survival

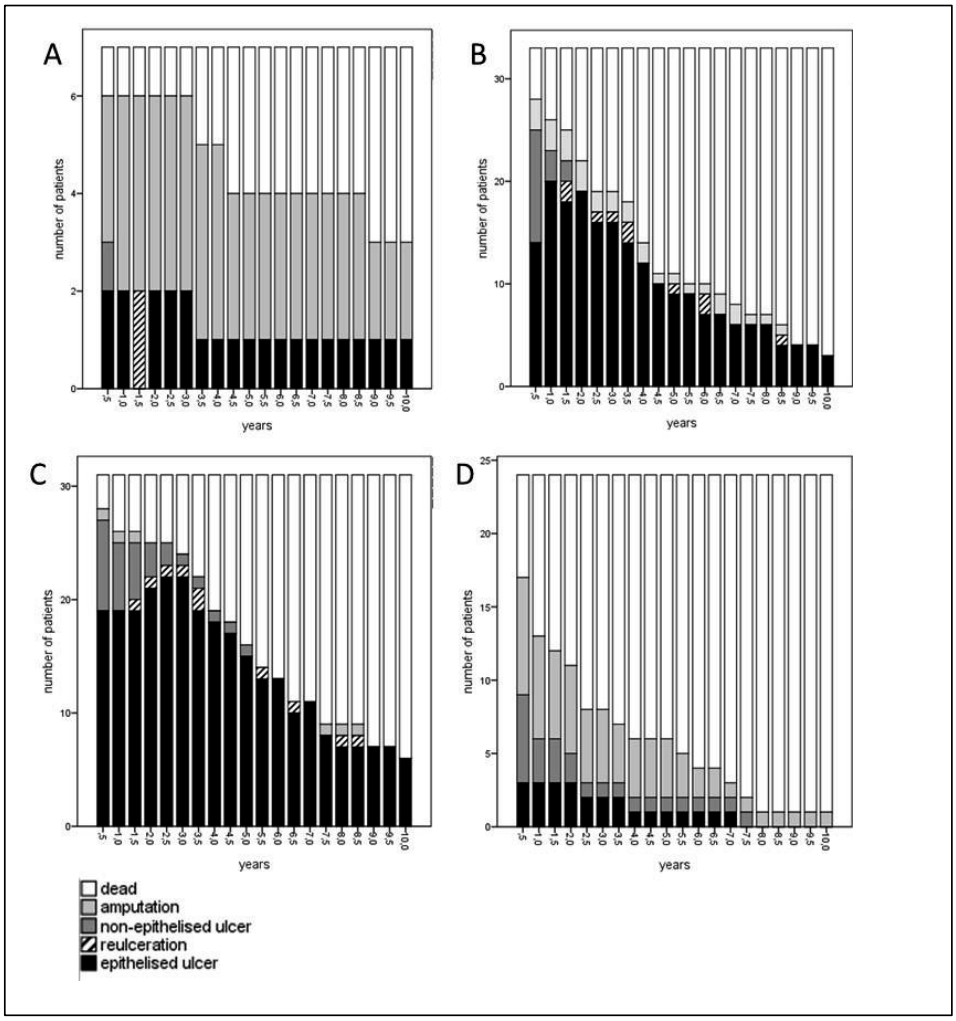

Figure 9. Outcome of the patients. A) Patients with type 1 diabetes, B) patients with type 2 diabetes, C) patients without diabetes, D) patients without revascularisation.

5.2.3 RISK FACTORS FOR AMPUTATION

In univariate analysis, amputation during the first year of follow-up was significantly associated with age ($p = 0.007$), CRP ($p < 0.001$), creatinine ($p = 0.043$), type 1 DM ($p = 0.003$) and uraemia ($p = 0.046$), as well as UT grade 3 depth ($p = 0.001$) and UT stage D infection ($p = 0.038$), in addition to being inversely associated with revascularisation ($p < 0.001$). An angiosome-oriented open arterial line was not significantly associated with major amputation within one year of follow-up. Table 30 shows the findings of multivariate analysis.

Table 30. Factors associated with major amputation during the first year of follow-up. Cox logistic regression analysis.

	Sig	HR	95%CI
Age	0.002	0.922	0.875–0.972
CRP	0.009	1.019	1.004–1.034
Revascularisation	0.003	0.169	0.045–0.636

Other parameters tested in the model were UT (University of Texas), sex, type 2 DM, DM, ever smoking, ulcer location in the toes, clinical infection UT D, angiosome oriented open arterial line, ulcer diameter
Sig significance; HR hasard ratio; CI confidence interval; CRP c-reactive protein

5.2.4 RISK FACTORS FOR DEATH

Death was significantly associated with type 2 DM (p = 0.028), CRP (p = 0.003) and creatinine (p = 0.043), and inversely associated with type 1 DM (p = 0.049) in univariate analysis. Table 31 shows the findings from multivariate analysis.

Table 31. Factors associated with death during the follow-up. Cox logistic regression analysis.

	Sig	Exp(B)	95%CI
Age	< 0.001	1.066	1.040–1.094
UT 3C or 3D	0.026	1.871	1.079–3.243
Uraemia	< 0.001	6.252	2.506–15.597
Diabetes	0.022	1.799	1.090–2.972
Revascularisation	0.012	0.497	0.289–0.855

UT (University of Texas)

5.2.5 ULCER HEALING AND RE-ULCERATION

At one year, 3/24 (13%) ulcers healed in patients who did not undergo revascularisation. As regards patients who underwent revascularisation, 2/7 ulcers healed among type I diabetic patients, 22/33 (67%) among type 2 patients and 20/31 (65%) among

nondiabetic patients. Out of the 54 patients whose ulcers healed during the follow-up, 43% developed a reulceration. The median healing times were 3.5 months (95% CI 0.7;6.3)in type 2 diabetic patients and 2.8 (95% CI 1.4;4.1) months in nondiabetic patients. The difference is not statistically significant.

An angiosome-targeted open arterial line was significantly associated with ulcer healing rate ($p < 0.001$), as was revascularisation as such ($p < 0.001$).

Walking capacity at six months and at one year was recorded in patients without amputation. Two of the 7 patients without revascularisation were able to walk more than a few steps. Of patients with revascularisation, both two with type 1 diabetes, 16/21 with type 2 diabetes and all 21 without diabetes were able to walk more than few steps.

5.3 FREE TISSUE TRANSFER WITH OR WITHOUT VASCULAR RECONSTRUCTION IN THE TREATMENT OF LARGE TISSUE DEFECTS (STUDY II AND III)

5.3.1 CHARACTERISTICS OF PATIENTS

The characteristics of patients are presented in Table 32 and Table 33 a-c. In Study II, 73% of the patients had diabetes. Type 1 diabetes was present in 26% of all patients and in 36% of the diabetic patients in Study II and 38% of the diabetic patients in Study III. In Study III, a significant difference between the groups related to the treatment of ischaemia was observed in creatinine values, toe pressures, ABI values, lesion locations and CRP-values.

Table 32. The characteristics of 81 lower extremieties of 79 patients with FTT and revascularisation in Study II. 73% of patients have DM.

Patient and lesion characteristics	DM 1	DM 2	no DM	sig DM1 vs DM2	sig DM1 vs no DM	sig DM2 vs no DM
n	21	38	22			
Median age, years (range)	47 (39-73)	65.5 (37-84)	68.5 (48-85)	p<0.001	p<0.001	NS
Male	57.1%	76%	54.5%	NS	NS	NS
History of smoking	33.3%	15.8%	45.5%	NS	NS	p=0.012
ASA 4	23.8%	31.6.%	13.6.%	NS	NS	NS
Elevated creatinine	57.1%	23.7%	4.7% n=21	p<0.01	p<0.001	NS
Renal transplantation	28.6%	2.6%	0	p=0.03	p=0.007	NS
CAD	42.9%	34.2%	27.3.%	NS	NS	NS
History of MI	23.8%	15.8%	4.5%	NS	NS	NS
CVD	4.8%	7.9%	9.1%	NS	NS	NS
Median BMI (range)	24 (18-31)	26 (19-36)	23 (16-32)	p=0.016	NS	p=0.002
History of BKA/AKA	28.6%	28.9%	9.1%	NS	NS	NS
Lesion in the leg	4.8%	7.9%	45.5%	NS	p=0.002	p=0.001
Lesion in the achilleus region	0	5.3%	4.5%	NS	NS	NS
Lesion in the forefoot	47.6%	39.5%	22.7%	NS	NS	NS
Lesion in the heel	33.3%	23.7%	9.1%	NS	p=0.051	NS
Plantar involvement	81%	54%, N=37	18.2%	p=0.041	p<0.001	p=0.007
Ulcer diameter > 10 cm	33.3%	51.3%, n=37	90%, n=20	NS	p=0.001	p=0.004
Pre-operative infection	57.1%	60.5%	40.9%	NS	NS	NS
Median pre-operative CRP (range)	38 (5-152)	39 (0-181)	38 (5-132)	NS	NS	NS
preceding revision	89%	81.6%	52%	NS	p=0.004	p=0.009
Bypass to flap	23.8%	18.4%	4.5%	NS	NS	NS
Pedal bypass	52.4%	47.4%	45.5.%	NS	NS	NS
Crural bypass	19%	21%	36%	NS	NS	NS
Popliteal bypass	4.8%	2.6%	4.5%	NS	NS	NS
PTA	0	7.9%	9.1%	NS	NS	NS
LD flap	66.7%	57.9%	36.4%	NS	p=0.047	NS

Table 32.
ASA = American Society of Anesthesiologists; CAD = coronary artery disease; MI = myocardial infarction; CVD = cerebrovascular disease; BMI = body mass index; BKA = below knee amputation; AKA = above knee amputation; CRP=C-reactive protein; PTA = percutaneous transluminal angioplasty; LD = latissimus dorsi; sig=significance; NS = not significant.
Nephropathy was defined as plasma or serum creatinine level exceeding the reference values of uraemia treated with dialysis. *Smoking during 5 preceding years was recorded.

Table 33 a. The characteristics of patients with DM in relation to the treatment of ischaemia in Study III.

Patient characteristics	All	Native artery (NA)	Correctable ischaemia (C)	Uncorrectable ischaemia (U)	p (NA vs C)	p (C vs U)	p (NA vs U)
n	63	19	32	12			
Median age, years	56 (21)	55 (17)	63 (24)	56 (19)	NS	NS	NS
Male	44 (70)	11	23	10	NS	NS	NS
Type 1 diabetes	24 (38)	8	12	4	NS	NS	NS
History of smoking	12 (19)	1	8	3	NS	NS	NS
ASA 4	14 (22)	2	8	4	NS	NS	NS
Elevated creatinine a	13 (21)	1	6	6	NS	.05	.01
Renal transplantation b	8 (13)	3	5	4	NS	NS	NS
Retinopathy	43 (81)c	14	21	8	NS	NS	NS
CAD	20 (32)	3	13	4	NS	NS	NS
History of MI	12 (19)	2	7	3	NS	NS	NS
CVD	7 (11)	1	4	2	NS	NS	NS
Median BMI (IQR)	24.5 (6.0)	24.5 (5.5)	25.0 (6.0)	23.0 (6.0)	NS	NS	NS
History of BKA/AKA	14 (22)	1	11	2	.02	NS	NS

Table 33 b. The characteristics of lesions in relation to the treatment of ischaemia in Study III.

Patient characteristics	All	Native artery (NA)	Correctable ischaemia (C)	Uncorrectable ischaemia (U)	p (NA vs C)	p (C vs U)	p (NA vs U)
Median pre-operative TP d	35 (33)	60 (43) e	30 (21) f	34 (45) g	.001	NS	.01
Median pre-operative ABI h	.99 (.78)	1.19 (.42) i	.71 (.84) j	.86 (.98) k	.01	NS	NS
Lesion in the ankle	7 (11)	5	2	0	NS	NS	NS
Lesion in the forefoot	30 (48)	7	14	9	NS	NS	.04
Lesion in the heel	18 (29)	4	13	1	NS	.04	NS
Plantar involvement	44 (70)	11	24	9	NS	NS	NS
Heel lesion > 10 cm	10 (16)	2	8	0	NS	NS	NS
Ulcer diameter > 10 cm	28 (44)	9	13	6	NS	NS	NS
Pre-operative infection	41 (65)	14	21	6	NS	NS	NS
Median pre-operative CRP	38 (46)	28 (5–38)	48 (53)l	37.5 (63.5)	.002	NS	NS

Table 33 c. The operation details of patients with DM in relation to the treatment of ischaemia in Study III.

Patient characteristics	All	Native artery (NA)	Correctable ischaemia (C)	Uncorrectable ischaemia (U)	p (NA vs C)	p (C vs U)	p (NA vs U)
Bypass to flap	11 (17)	5	6				
Pedal bypass	23 (37)	23					
Crural bypass	13 (21)	8	5				
Popliteal bypass	1 (2)	1					
PTA	3 (5)	3					
LD flap	38 (60)	12	20	6	NS	NS	NS
Median flap OT, min	276 (53)m,n	280 (48)o	323 (60)p				
Median vascular OT, min	177 (61)q	197r					
Median combined OT, min	354 (154)s	387 (80)t	356 (104)u				

Tables 33a-c:
Note. Data are given as *n* (%) or median (IQR).
IQR = interquartile range; ASA = American Society of Anesthesiologists; CAD = coronary artery disease; MI = myocardial infarction; CVD = cerebrovascular disease; BMI = body mass index; BKA = below knee amputation; AKA = above knee amputation; TP = toe pressure; ABI = ankle brachial index; CRP=C-reactive protein; PTA = percutaneous transluminal angioplasty; LD = latissimus dorsi; OT = operation time; NS = not significant.
aTwo patients were uraemic.
bNormal serum creatinine, four of 12 of patients with renal transplant had elevated creatinine.
c*n* = 53; .d*n* = 41; .e*n* = 11; f*n* = 23; g*n* = 7; h*n* = 50; i*n* = 13; j*n* = 26: k*n* = 11;l*n* = 31; m Including PTA.
n*n* = 14; o*n* = 11; p*n* = 2; q*n* = 11; r*n* = 1; s*n* = 5; t*n* = 21; .u*n* = 10.

5.3.2 COMPLICATIONS

Healing after the 98 FTT was uneventful in only 17% of the operations when postoperative 30-day amputations, flap losses and other local complications, as well as donor site complications, general complications and mortality were considered. The most common 30-day postoperative complications after the 98 FTT operations were minor flap edge necrosis and an infection (Table 34). Major postoperative complications such as death, amputation, flap loss, flap or vascular salvage operation and general complication were avoided in 49% of the flap operations. For the patients included in Study II with combined FTT and vascular reconstruction, the mean hospital stay was 70 days.

During the 30-day postoperative period, 1-4 reoperations were required in 58% percentof the 98 FTT operatons (Clavien-Dindo grade III) (Table 35 and Table 36). Fifteen legs were amputated within 3 postoperative months and 13 legs thereafter. Persisting tissue destruction and vascular problems were the most frequent causes (Table 36 and Table 37).

Seroma of the donor site was observed 21 cases and infection, bleeding and failure to heal in four cases. In addition, three hernias and two hypertrophic scars were encountered. Tight scar, chronic pain, unsuccesfull flap elevation and local necrosis of the rectus fascia were reported once each. Seroma was mostly encountered after latissimus dorsi muscle elevation, hernias after rectus abdominis muscle elevation and slow healing after forearm flap elevation.

The most frequent general complications were cardiac insufficiency and acute myocardial infarction. The three-month postoperative mortality was 4.9%.

Table 34. Local complications of the 98 flaps. No more than two complications per operation were recorded here.

Complication	
none	29
flap vein thrombosis	6
flap edge necrosis	32
vascular reconstruction failure	4
new ulcer	2
wound infection	15
osteitis	1
haematoma	6
partial necrosis of the flap	7
toe amputation	3
fistula problem	1
arterial anastomosis problem	5
venous anastomosis to artery	1
seroma	1
venous congestion	1

Table 35. Postoperative complications related to microvascular FTT within the first 30 days in 98 FTTs in Studies II and III.

	n	local compl.	general compl.	Clavien-Dindo III	partial flap loss	postop. flap loss	postop. amputation	postop death
DM I	27	21	6	14	1	6	3	0
DM II	49	35	14	27	3	8	5	2
no DM	22	13	4	15	2	4	2	1
total	98	69	24	56	7	17	10	3

compl. =complication, postop=postoperative

Table 36. Lower extremity major complications related to combined vascular reconstruction and microvascular FTT for CLTI within the first 3 months in Study II

Complication	n	Salvage operation	Flap loss after salvage operation	Amputation after salvage operation	All 3-month flap loss	All 3-month amputation
Bypass occlusion	5	3	0	2	1	3
Flap artery thrombosis	2	2	0	1	0	1
Flap vein thrombosis	11	8	1	3	4	3
Flap vein and artery Thrombosis	3	2	1	0	1	1
Persisting infection or gangrene of the foot	7	0	0	0	0	7
Total	28	15	2	6	6	15

Table 37. The reasons for late major amputations after 3 postoperative months in Study II

	Number of legs
Vascular graft thrombosis	4
Early flap loss, no healing	3
No healing despite a vital flap	2
Ischaemic tissue defect in locations remote from the flap	2
Late flap Necrosis	1
Vascular prosthesis infection after multiple reconstructions during 7 years	1

5.3.3. OUTCOME

In Study II, the one- and 5-year limb salvage rates were 73% and 66%, survival rates 91% and 63%, and amputation-free survival rates 70% and 41%, respectively (Figure 10).

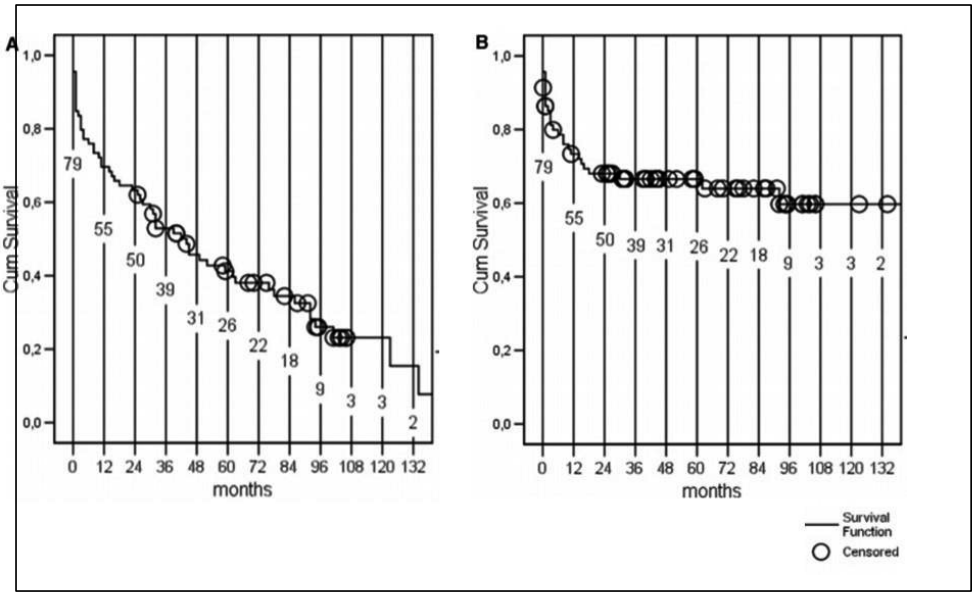

Figure 10. Limb salvage (A) and amputation-free survival (B) of 79 patients in Study II. (Reproduced with permission from Tukiainen et al. 2003)

In Study III, the leg salvage rates at 1, 5 and 10 years were 94%, 94% and 87%, respectively, in group NA; 71%, 65% and 65%, respectively, in group C; and 50%, 50% and 50%, respectively, in group U. The amputation-free survival rates at 1, 5 and 10 years were 90%, 79% and 63%, respectively, in group NA; 66%, 25% and 18%, respectively, in group C; and 50%, 42% and 17%, respectively, in group U. (Figures 11 and 12.)

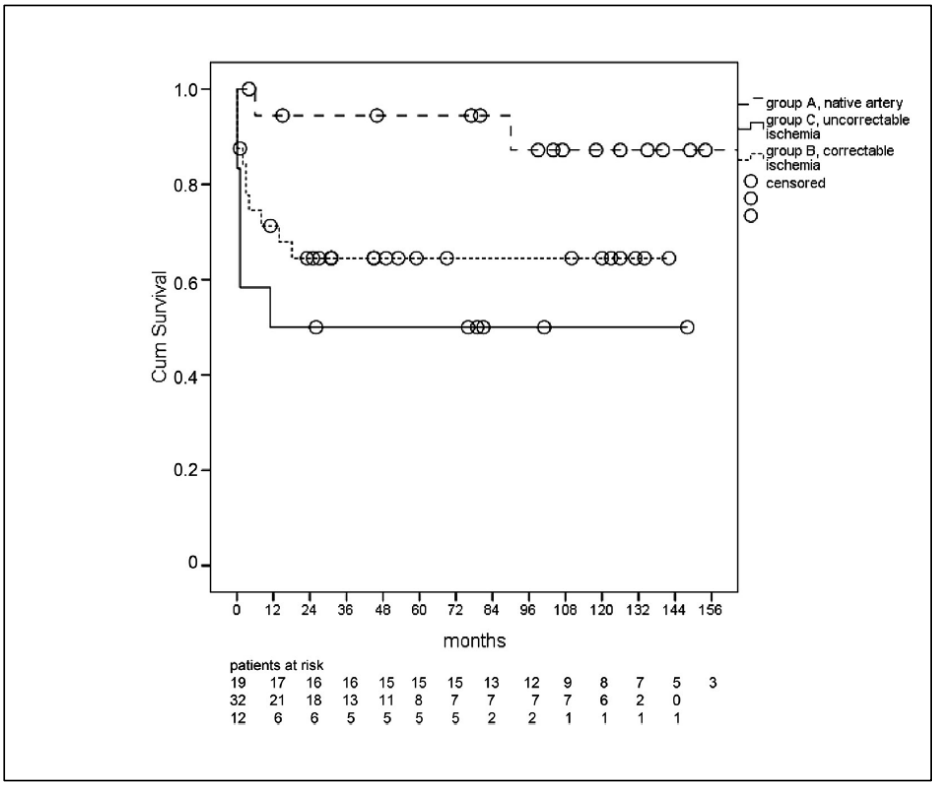

Figure 11. Leg salvage. Differences between the groups A and B as well as between A and C were significant ($p<0.001$ and $p=0.01$). Reproduced with permission from Kallio et al. 2003.

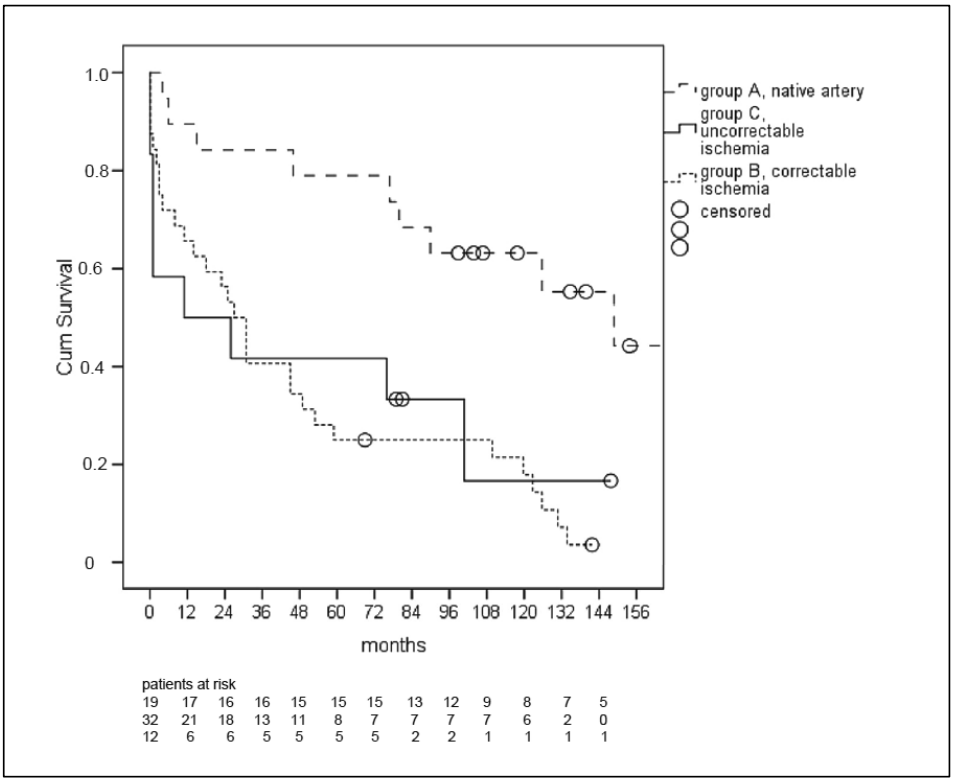

Figure 12. Amputation-free survival. The diggerence between the groups A and each of B and C were significant ($p<0.001$ and $p=0.01$) Reproduced with permission from Kallio et al. 2003.

In Study II, 52% of the patients were able to ambulate in the community and in the household with the preserved leg at two years (Figure 13). In Study III, healing within 1 year, with full epithelisation for at least 6 months, was achieved by 43%, 45% and 18% of the patients in groups NA, C and U, respectively.

Minor ulcer recurrence was observed in 54% of patients with primary skin healing for at least six months in Study II.

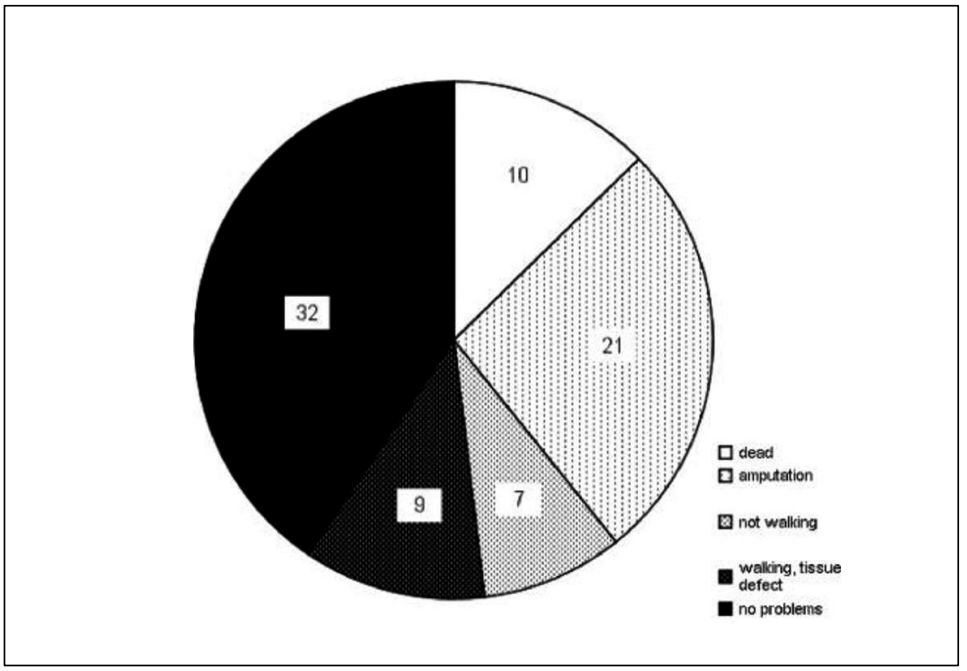

Figure 13. Outcome of the 79 patients at two years. Reproduced with permission from Tukiainen et al. 2003.

5.3.4 PREDICTORS OF OUTCOME

In Study II, male sex and an American Society of Anesthesiologists (ASA) score of 4 were associated with an increased risk of death, whereas diabetes was not. The involvement of the heel, mostly with calcaneal osteomyelitis and a large defect size, predicted major amputation (Table 38).

In Study III, major amputation was associated with smoking (risk ratio [RR] 3.09, 95% CI 1.8–5.3), heel ulceration (RR 2.25, 95% CI 1.1–4.7), nephropathy (RR 2.24, 95% CI 1.04–4.82), and an ulcer diameter of > 10 cm (RR 2.08, 95% CI 1.03–4.48) (Figure 14).

The most morbid patients, with an ASA score of 4, in Study III had complications frequently, and their 5-year survival was 45%. A learning curve was seen, and fewer ASA 4 patients were operated on during the later years, resulting in lower mortality (Figure 15).

Table 38. Cox regression analysis: variables associated with death and amputation during the follow-up

Variable	Hazard ratio	95% confidence interval	p
Association with death			
Male sex	2.2	1.1–4.4	0.03
ASA 4 vs ASA < 4	2.6	1.4–5.0	0.003
Coronary artery disease	2.2	1.2–4.2	0.01
Contralateral amputation	2.5	1.3–4.9	0.006
Association with amputation			
Location in the heel	2.5	1.2–5.5	0.02
Diameter exceeding 10 cm	2.5	1.0–5.9	0.04

Other variables tested in the analysis: age(years), type 1 DM vs type 2 DM, previous coronary artery bypass grafting, cerebrovascular disease, nephropathy, previous renal transplantation, smoking during 5 preceding years, BMI, preoperative CRP, forefoot as a specific location, leg as a specific location, plantar involvement, chronic wound as a specific indication, graft infection as a specific indication, latissimus dorsi flap, forearm flap, and availability of recipient artery for bypass.

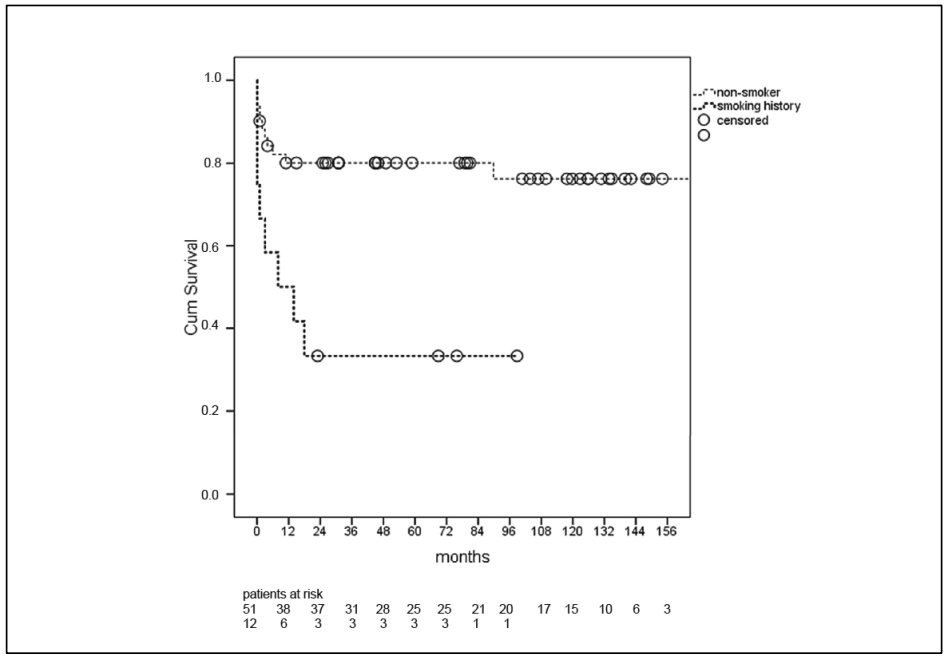

Figure 14. Leg salvage in smokers and non-smokers (p=0.01). Reproduced with permission from Kallio et al. 2003.

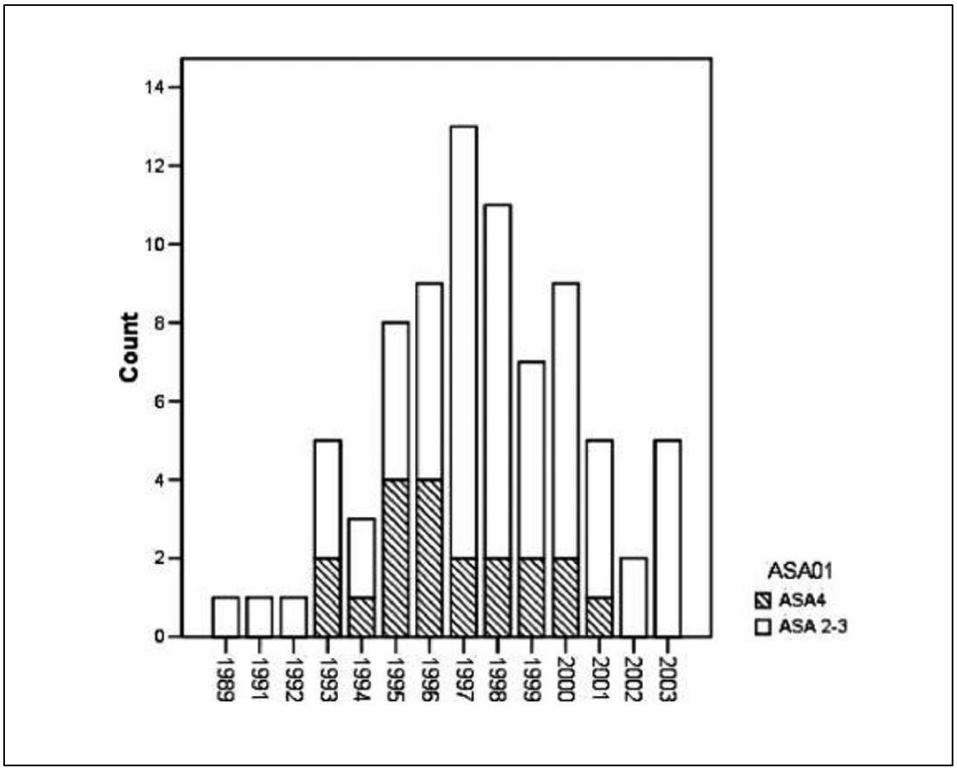

Figure 15. ASA 4 patients in Study II. Reproduced with permission from Tukiainen et al. 2003.

6 DISCUSSION

6.1 LIMITATIONS OF THE STUDY

The cohorts were quite small for generalisable conclusions on outcomes or for running multivariate analyses in Studies I–IV. Indeed, the multitude of variables affecting the outcome causes challenges for implementing studies investigating ulcers (Gershater 2009). Ulcer characteristics (depth, size, location), the side and number of ulcers, additional aetiologies (type 1 and type 2 diabetes, LEAD, neuropathy, nephropathy, infection, oedema, rheumatoid diseases, gout, etc.), as well as patient demographics and characteristics (age, sex, weight, smoking) vary. Furthermore, the small number of patients made type 2 error probable. Long-term comparative survival data was statistically insignificant in many subgroups due to high mortality and amputation rates, leaving a small number of patients for the analysis. To form a uniform group for studying the effect of factors or interventions in patients with ulcers, considerable effort and very large groups of patients would be needed.

In Study IV, a thorough clinical examination was performed at baseline, but ABI and TP measurements were not always available due to frequent admittance out of office hours. Since the implementation of our study, the classification and treatment of ischaemic ulcers have taken many steps of development. However, the ulcer characteristics were carefully recorded prospectively. Basic findings, such as the severity of infection and ischaemia and the anatomical depth and location of the ulcer, are still regarded important elements in defining the outcome of an ulcer (Mills et al. 2014).

All the studies included herein are clinical cohort studies, as the available resources were insufficient for running randomised studies. Furthermore, the number of FTT operations is limited and randomisation would have necessitated a multicentre study. In Studies I and IV, the baseline data was collected prospectively, but the follow-up was retrospective in all studies. In Study IV, only 30% of the patients attended a planned control visit. Therefore, follow-up data in Studies II, III and IV were checked from the patient records from all health care levels. All data were based on active recordings. For example, an ulcer was not regarded as healed if it was not mentioned or there were no more visits. In contrast, a recording of healing was required.

In Study I, the Helsinki Diabetes Association register may not have contained a fully representative population from the region. On the national level, 62% of type II diabetic patients in 1988 were women. In thebaseline cohort of our study, 43% of the patients without LEAD and 50% of those with LEAD were women. The median age of Finnish diabetic men in 1988 was 66 years and of diabetic women 73 years. (Niemi and Winell 2005.) The patients in the current study were younger. The ABI values between 0.9 and 1.15 might have included falsely elevated values.

Due to the retrospective and descriptive nature of Studies II and III, generalisation of the results requires caution. However, the outcome estimates are similar when compared to other large series of diabetic patients (Randon et al. 2010, Oh et al. 2012). A study arm for collecting a control group of patients with lower extremity major amputations was initiated. However, it proved difficult to find patients in a similar general condition compared to patients undergoing FTT. In another Finnish study, 57% of the patients survived longer than one month after major amputation (Remes et al. 2008).

6.2 DEVELOPMENT AND RISK FACTORS OF LEAD IN TYPE 2 DIABETIC PATIENTS

In Study I, a long follow-up and wide package of investigations enabled us to show the development of LEAD and other cardiovascular complications and weigh different risk factors. Half the patients with LEAD died during the follow-up. Concurrently, the proportion of patients with LEAD increased further from 16% to at least 31% at follow-up. Decreased ABI values predicted death in diabetic patients with no other signs of cardiovascular disease concordantly with earlier studies among the general population (Leng et al. 1996). The risk factors for LEAD were different at baseline and at follow-up. LDL cholesterol and HDL cholesterol were significant predictors of developing LEAD, especially in patients with less fatal cardiovascular complications. At baseline in 1984, LDL cholesterol levels were high compared to modern standards, ranging from 2.11 to 7.62 mmol/l. The medications as well as operative care have developed since then.

Secondary prevention was already suggested for patients with asymptomatic LEAD in the 1990s. (Leng et al 1996). Nevertheless, until recently, asymptomatic LEAD and claudication were considered relatively benign complications of cardiovascular disease, with a 1% major amputation risk in patients with claudication (Norgren 2007). Currently, the high morbidity of patients with LEAD has gradually been fully recognised, and the treatment of risk factors is emphasised (Ögren et al. 2005, Diehm et al. 2009, Aboyans et al. 2018). Indeed, in the Fourier study, LDL cholesterol lowering from a median of 2.4 mmol/l to a median of 0.8 mmol/l with evolocumad, an effective cholesterol-lowering medication, induced a significant risk reduction in MALEs (major adverse limb event) and major adverse cardiovascular events (MACE)s among patients with LEAD, with and without previous cardio- or cerebrovascular disease. The event-reducing effect was almost linearly related to LDL cholesterol levels down to 0.26 mmol/l. (Bonaca et al. 2017.)

6.3 ISCHAEMIC ULCERS

People and their needs are different. A small superficial ulcer in a person with a poor general condition needs a different approach than an infected large tissue defect of a person with an active life. For one person, a stump or a foot with a quiet ulcer and ability take a few steps is an optimal solution, while for somebody else, this would entail amputation and a functional prosthesis, allowing active mobility. An increasing group of patients are not able to weigh risks and benefits of treatment or the desired aims of treatment themselves because of dementia. More data is needed to find the best solution for individual patients but also for directing the resources effectively.

Selecting a clinically significant outcome, such as ulcer healing, leg salvage, reulceration or AFS, is crucial. At present, MALEs and MACEs are widely used end points. Some outcomes may be useful for other study purposes, such as patency for the development of revascularisation techniques and a diminishing wound surface for the testing of new local treatment methods. Whether the outcome is determined for the ulcer, for the leg or for the patient needs to be considered. Ulcer healing and reulceration requires long and strict follow-up and consistent criteria.

The cohort in Study IV contained consecutive patients referred for vascular consultation. The long-term outcome of patients with ischaemic ulcers was poor. A total of 11% of the original cohort was alive with the leg intact after 10-year follow-up. Type 1 diabetes was associated with major amputation within 1 year of follow-up, whereas type 2 diabetes was associated with death during the follow-up. Leg salvage was similar among type 2 diabetic patients and nondiabetic patients after revascularisation. Patients without revascularisation had a very poor outcome. This finding is similar to that of Lepäntalo and Mätzke (1996). Type 1 diabetic patients with cardiac and renal complications were at a very high risk of amputation due to ischaemic ulcers.

Ulcer healing at one year was similar in nondiabetic (65%) and type 2 diabetic patients (67%) with revascularisation. A later cohort from our clinic showed 63% and 87% healing of the lesions after bypass surgery in diabetic and nondiabetic patients, respectively. However, incisional wounds and type 1 diabetic patients were also included. (Söderström et al. 2008.) A systematic review reported an ulcer healing rate of 60% in diabetic patients at one year after endovascular revascularisation but observed substantial variation in figures, probably mostly due to heterogeneous material and differences in reporting (Hinchliffe et al. 2016). Indeed, a surprise in our projects was that ulcer healing was poorly recorded. The data was tracked all the way down to hand-written home care notes until a specific positive or negative recording was found.

6.4 REVASCULARISATION

A more favourable outcome in terms of both leg salvage and ulcer healing among patients who underwent revascularisation than those remaining without revascularisation was observed in this thesis. Angiosome-oriented revascularisation was not associated with amputation. In contrasrt, angiosome-oriented was associated with ulcer healing. Notably, the division into angiosomes was performed post hoc. Better healing and leg salvage rates in patients with more direct revascularisation, especially endovascular, to the ulcer area have been reported in many studies (Spillerova et al. 2016, Zheng et al. 2016, Alexandrescu et al. 2019, Jongsma et al 2017). However, the actual circulation in the angiosome and its effect on ulcer healing is challenging to evaluate. Endovascular treatment and open surgery may have different haemodynamic effects (Spillerova et al. 2016). Anatomic variations in the calf and foot arteries exist, and the collateral network is individual. Moreover, angiography ignores haemodynamic circumstances. No general validated definition or classification exists for the quality of collaterals. Furthermore, ulcers can involve more than one angiosome, and, on the other hand, the feeding areas of arteries overlap. (Attinger et al. 2006, Spillerova et al. 2016.) Therefore, identifying the angiosome requiring revascularisation is often ambiguous (Aerden et al. 2014). Furthermore, the endless variation in the characteristics of ulcers and patients easily make comparisons biased (Conte et al. 2019).

A small stable ulcer rarely deteriorates acutely (Barshes et al. 2014), and spontaneous healing of ulcers in ischaemic foot also does occur (Marston et al. 2006). Revascularisation is not always necessary for the healing of small non-infected ulcers (Cull 2014, Conte et al 2019). However, vascular supply and infection seem to be the main factors influencing the healing of ischaemic diabetic foot ulcers, and the UT and WIFI classifications can be used to predict major amputations (Cull et al. 2014, Armstrong et al. 1998).

Methods for evaluating the haemodynamic conditions necessary for ulcer healing are incomplete. Optimally, perfusion would be investigated during the revascularisation procedure, and further revascularisation should be attempted if low-perfusion areas remain. Transcutaneous oxygen pressure ($tcpO_2$) measurements and Indocyanine green fluorescence imaging (ICG-FI), noninvasive methods for studying the oxygenation of tissue and the distribution of arterial circulation, have their limitations. They are time-consuming and especially ICG-FI is subject to wide interpersonal variety, with no universal reference values (Hinchliffe et al. 2016, Conte et al. 2019, Antonopoulos et al. 2019).

6.5 TREATMENT OF LARGE TISSUE DEFECTS

Deep infections, ischaemic ulcers and gangrene, which often necessitate revisions and foot-level amputations, result in large tissue defects in diabetic patients (Lombardo et al 2014, Hong et al. 2011). Deep infections are typically encountered in diabetic patients, and roughly half of the patients with ischaemic ulcers have diabetes (Prompers et al 2007, Söderström et al. 2008). Combined ischaemia and infection pose a great risk on leg salvage (Cull et al. 2014, Armstrong et al 1998). In the present thesis, a third of all tissue lesions in diabetic patients who were referred to a vascular surgeon were deep and infected. Revascularisation and CRP were associated with major amputation and ulcer healing time. Furthermore, 84% of the diabetic patients who underwent FTT had undergone preceding revisions or minor amputations, and roughly 60% had a foot infection in the background.

Many alternatives for closing the defects and enhancing healing are available: NPWT, skin grafting, skin and dermal substitutes and local flaps. These methods are sometimes insufficient for covering large defects that expose bones and tendons or are located on weight-bearing surfaces. Moreover, in the presence of LEAD and diabetes, local flaps tend to have a high failure rate (Baumeister et al. 2003). Occasionally, a major amputation is inevitable. However, amputation may also be the best treatment option. If the capacity for rehabilitation is good, ambulation with a prosthesis may offer better functional ability than a deformed, easily ulcerating foot. Comorbidities, such as coronary artery disease, nephropathy and obesity, are common in diabetic patients and may be an impediment to major surgery (Krempf et al. 2010). Sometimes comorbidities cause special challenges. For a patient removed from the waiting list for renal transplantation or cardiac procedure because of an ulcer, the time-consuming effort required to get a severe ulcer to heal can be a catastrophe. According to Attinger and Brown, “function and quality of life are the outcomes of interest and may be maximised through either limb salvage or amputation” (Attinger et al. 2012).

Below-knee amputation gives a reasonable opportunity for ambulation with a prosthesis. Still, elderly and multimorbid patients often lack the capacity for rehabilitation required for becoming successful users of prosthesis.Above-knee amputation is a simple and quick procedure, and the healing is less complicated than after below-knee amputation. Therefore, it is frequently chosen for patients with a greatly reduced general condition and limited mobility. The functional aim is often independent or assisted mobilisation with a wheelchair. Palliative care without amputation may be considered in patients with a very poor general condition. Complicated tissue defects in the diabetic foot can be overcome with vascular and plastic surgeon teamwork in selected cases.

6.6 FTT

Sustaining teamwork between vascular and plastic surgeons resulted in the thus far largest cohort of patients with combined FTT and vascular reconstruction for limb-threatening tissue defects and ischaemia. The amputation-free survival rate was 41% at five years. Excellent amputation-free survival at five years can be expected in diabetic patients with a native artery open to the foot. At ten years, amputation-free survival was still 63%. In comparison, amputation-free survival was 51% at five years in patients with ischaemic lesions treated with a similar technique (Randon et al. 2009). In the US, a limb salvage rate of 65% and a survival rate of 67% at 5 years were observed (Moran et al. 2002). The three-year amputation-free survival was 56% in a cohort of diabetic patients (Randon et al. 2010). According to our findings, even in the absence of options for revascularisation, moderate AFS can be reached by careful individual assessment.

Diabetes was not associated with amputation or death after FTT in our study. Large defects with a diameter exceeding 10 cm and heel ulcers in ischaemic extremities, and in diabetic patients, smoking and nephropathy, were associated with amputation. Severe morbidity, coronary artery disease, male sex and age were associated with death. In Belgium, renal insufficiency and earlier contralateral limb amputation were risk factors for amputation and in the US, diabetes combined with renal insufficiency and diabetes alone. (Randon et al. 2009, Randon et al. 2010, Illig et al. 2001.) The risk factors for death were previous foot surgery in the Belgian study and diabetes and diabetes combined with ESRD in the American study.

Careful patient selection and planning are crucial. A multidisciplinary team with a vascular surgeon, plastic surgeon, anaesthesiologist, internist and infection specialist is invaluable in the planning. The cardiovascular risks should be investigated and a cardiologist consulted, as necessary. Uraemic and ASA 4 patients are usually no longer considered for FTT in our clinic. Smoking is also a strong argument against the operation, and every effort should thus be taken to support the patient in stopping smoking. It is important that all aspects of major surgery and long rehabilitation are discussed thoroughly with the patient before the decision to operate. It should be noted that the achievable walking distance can be limited and that ulcer healing is often time-consuming and reulcerations occur.

In patients with a successful outcome, a good level of ambulation was achieved. Fifty-nine percent of patients who survived and 89% of patients with limb salvage were ambulant at two years. All surviving patients returned home. Especially patients whose independent living is depending on the few steps taken with their own limb benefit from this operation. The mobility after FTT might be compared to the mobility of patients returning home after major amputation. Of patients who underwent major amputation due to ischaemic or diabetic complications, 22%–45% gained community or household ambulation. (Kanellopoulos et al. 1996, , Remes et al. 2009.) In a Finnish study, 43% of patients surviving after major amputation returned home. However, 72% of the patients

who were discharged and returned home gained ambulation, with only 33% being able to ambulate outdoors. (Remes 2009.) Diabetes was associated with successful prosthesis usage. A high rate of diabetes in younger age groups may explain this. Of patients under 65 years, 72% had DM (Remes et al. 2009).

The rehabilitation aiming at walking ability with a prosthesis requires good physical and mental capacity from the patient. Wearing prosthesis at nighttime is burdensome. Such diseases as rheumatoid diseases and arthrosis may hinder prosthetisation. In diabetic patients, visual impairment is frequent, as is a history of stroke with reduced strength and coordination. In elderly individuals, atrophy and contractions in the hand musculature and arthropathies can make the wearing a prosthesis or the utilisation of devices difficult. Moreover, balance can be insufficient. These conditions may favor FTT over a major amputation in patients with adequate general condition.

However, the groups of patients with FTT and major amputation are not comparable. The general condition of patients undergoing major amputation is, on average, considerably poorer than that of patients undergoing profound evaluation before FTT reconstruction (Elgzyri et al 2013, Noronen et al. 2017). Moreover, many amputations are performed as a last option when revascularisation is considered too risky.

In the studies included in this thesis , recovery from the FTT operation was uneventful in only 17% of the patients. Fifty-eight percent of the legs required reoperations. After below-knee amputation, stump problems delaying rehabilitation are also common. Problems in healing easily lead to femoral amputation, which is rarely a realistic premise for ambulation with a prosthesis.

In consequence, the choice of treatment is based on individual assessment: the patient's needs as regards ambulation, the severity of the tissue defect, general condition and the patient's cooperation and motivation are important aspects to be considered. Teamwork and experience are essential for the successful treatment of large ischaemic diabetic foot defects.

6.7 FUTURE PERSPECTIVES

A multitude of variables affecting the outcome cause challenges for implementing studies on ulcer healing. Therefore, large cohorts comprising all care levels are needed (Gershater et al. 2009). Ulcer healing and reulceration require long and strict follow-up and consistent criteria. Prospective register-based data is invaluable (Öien et al. 2016). In the future, separate analyses of type 1 and type 2 diabetic patients may offer more accurate outcome data.

With modern technologies, limb salvage can often be achieved despite a complicated situation. More sophisticated endovascular techniques – also combined with FTT, perforator flaps, bio-engineered skin substitutes, negative pressure devices and compression pumps – have become additional options in everyday practice since the studies included herein were conducted (Oh et al. 2012, Huang et al. 2014, Game et al. 2016, Liu et al. 2018, Conte et al 2019). The potential of stem cells and growth factors to enhance ulcer healing in diabetic patients is being studied actively (Gorecka et al. 2020, Lopes et al. 2018). However, the current situation is not yet acceptable: an immense amount of resources are spent on unhealed ulcers, and ulcers continue to cause suffering and a reduced quality of life for patients. Indeed, 783 transfemoral and 344 transtibial amputations were still performed in Finland in 2018. The overall duration of diabetes will increase due to the growing incidence, the onset of type2 diabetes at a young age, and decreased mortality. This might affect the future incidence of diabetic complications in the general population. (Gregg et al. 2016.) Great future potential lies in prevention: the prevention of diabetes, LEAD, conditions predisposing to ulcers, as well as of delays in proper treatment and of reulceration.

Tools to prevent type 1 diabetes are yet to make a breakthrough. In the meantime, the outcome of type 1 diabetics with ulcers emerges as a meaningful field of research. In contrast, the prevention of type 2 diabetes is often possible by increasing mobility and by weight control, and the risk factors of LEAD are well known. However, changing people's lifestyle and habits has proven difficult. (Fogelholm et al. 2017.)

Effective ways to influence people lifestyle remain to be discovered. Obviously, interdisciplinary collaboration is necessary, as is changing behaviour in the entire society.

7 CONCLUSIONS

1) One in five patients aged 60 years with type 2 diabetes develop new peripheral arterial occlusive disease (LEAD) during 11-year follow-up. High serum LDL and low serum HDL cholesterol are risk factors for incident LEAD.

2) Vascular reconstruction combined with microvascular free-tissue transfer (FTT) offers an option for advanced limb salvage in a selected group of patients with a critically ischaemic large tissue defect. Risk factors for a modest outcome are poor general condition, the involvement of the heel frequently complicated by osteomyelitis and an extensive defect. In these circumstances, primary amputation might be suggested instead of extensive reconstructive surgery.

3) In diabetic patients who have a native in-line artery to the ulcer area, extensive complicated foot defects may be covered by FTT, with excellent long-term amputation-free survival despite diabetic comorbidities. In the presence of occlusive disease and ischaemia, limbs may also be salvaged with combined FTT and vascular reconstruction in non-smokers and in the absence of a very extensive heel ulcer. Occasionally, even without the possibility of direct revascularisation, amputation is avoidable with FTT.

4) The ten-year amputation-free survival rate is approximately 10% in patients with ischaemic ulcers attending a vascular surgical consultation. The long-term amputation-free survival of patients who are not candidates for vascular reconstruction is dismal. The risk factors for amputation include unreconstructable vascular disease, high CRP and uraemia whereas type 2 diabetes remains insignificant. Instead, type 2 diabetes is associated with mortality. The role of type I diabetes is ambiguous. A substantial proportion of the patients whose ulcers heal during the follow-up develop a reulceration.

ACKNOWLEDGEMENTS

This thesis work was carried out at the Department of Vascular Surgery and Plastic Surgery at Helsinki University Hospital during 1992–2020.

I have been privileged in having an opportunity to work and live with so many enthusiastic, charismatic and encouraging people. I wish to express my special gratitude to:

Professor emeritus Mauri Lepäntalo, my supervisor, for providing me with this project and for the never-failing optimism and flourishing ideas. You created a humane atmosphere at the clinic, which persists to this day and still attracts young colleagues to join the team. You were ahead of the times with your attitude of not seeing problems, just challenges, and, time after time, you made me believe that they can be overcome.

Professor Erkki Tukiainen, my co-supervisor throughout these years, for sharing your knowledge, vast experience and special archives in the field of microvascular tissue transfers, as well as for your helpfulness and for always having time for guidance and discussions.

Professor Maarit Venermo for accepting the baton of supervisor from Mauri and being encouraging, optimistic and helpful, as well as pragmatic and project-oriented – all at once. With your guidance and cooperation, the finish line was within reach.

Professor emerita Sirpa Asko-Seljavaara for your support for the project and for your effort for plastic surgery in Finland, which for its part was a basement for these studies among many others.

Professor Mauro Gargiulo for the honour of having you as the opponent and for the flexibility of arrangements during the corona crisis.

Docent Eva Saarinen for thoroughly inspecting the manuscript and giving invaluable suggestions for the revision from commas to the composition of the thesis.

Docent Ilkka Kaartinen for your prompt advice as regards revising the thesis and for sharing important plastic surgical viewpoints.

DMSc Carol Forsblom for being the cornerstone of my research career by teaching me everything from statistics and data processing to protocols and details in diabetes research. Through all these years, you have always been available when I have had questions. I admire your enthusiasm and profound knowledge in so many fields.

Professor Per-Henrik Groop for sharing your vast knowledge in diabetes research, and for your time whenever needed. Your optimism, encouragement and understanding have been important in this process.

Professor Leif Groop for teaching us with a scientific touch starting from medical school and for collaborating in the diabetes study.

Docent and dear colleague Pirkka Vikatmaa for helping me find the missing thread in my work, for your application of critical thinking also in everyday work, as well as for your good sense of humour that has delighted us all at the clinic on many occasions.

Docent and dear colleague Ilkka Kantonen for the endless dedication to clinical work, which partly enabled the accumulation of the exceptional material to be studied in this thesis. Besides being a wonderful role model for all vascular surgeons and a sincere colleague to work with you are always eager to share your knowledge.

Eeva Parviainen for the accurate proofreading of the manuscript with a flexible schedule.

MSc Jukka Ollgren for the statistical advice, and Marita von Bell and Päivikki Määttälä for the vascular laboratory measurements in Study I.

The patients who participated in the studies.

The Chief of the clinic, Anders Albäck, for keeping the wheels turning at the clinic every day with fair, pragmatic and fact-based guidance and for pushing the clinic towards front line of new developments.

Docent Aarno Lehtola and Docent Mikael Railo for your guidance in the vascular surgical world at the Maria Hospital. I performed my first ADP bypass there, guided by Aarno, Mikael's father's loops with double images on my nose. Vesa and Tuula Juutilainen for sharing your experience in the field of diabetic foot and family life in a collegial manner.

Orthopaedist Leo Strid in Lappeenranta and General Surgeon Pasi Kaartinen in Savonlinna for the collegial relationship and for sharing your experience and inspiration.

Dear colleagues Eeva-Maija, Pekka, Petteri, Sani, Sailaritta, Elina, Katariina L, Maria, Karoliina, Katariina N, Ivika, Patrik, Matti, Sari, Riikka and all the other colleagues for sharing the delights and sorrows of our challenging and interesting but also demanding and burdensome work by discussing it, joking about it or sometimes by not saying anything. Maria and Katariina N are also thanked for the good advice on this thesis project and Maria for taking care of so many things on behalf of us all.

Study Nurse Anita Mäkelä and Chief of Department Sorjo Mätzke for your valuable help and advice and Secretaries Leena Multanen and Heidi Lunden for the fluent arrangements over the years. Tissue Viability Nurse Tiina Pukki and Podiatrist Hanneli Saaarikoski for inspiring collaboration – and Hanneli also for your assistance in making the cover of the thesis.

The staff of the Vascular Surgical Clinic, for good collaboration and dedication to the indispensable work.

Our dynamic Wound Center team – Heli, Kirsi, Heini, Opri and Tuula – Kirsti and everybody in the wound network – for the mutual efforts towards preventing and healing the ulcers and for working with an inspiring and innovative team spirit.

My fellow medical students, the lovely “Chestoladies” Riitta, Maarit, Laura, Minna, Tea, Tove and Kaija, as well as Mari, Ressu and Vesa and many others with whom I will hopefully always have a special relationship.

My fantastic friends Sani, Heikki, Kirsi, Riitta, Jannu, Kassu, Kaija-Leena, Gesa, Christian, Jarna and Heli for sharing some of the most important moments of life and for your constant support.

My parents-in-law, Leena and Tapani, and my sister-in-law, Ilona, for intriguing discussions and for the invaluable help with the children.

My wonderful sister Senna for sharing, in harmony, a considerable part of my life and obligations, and Jarmo for always being helpful and communicative.

My mother Raita and father Arto for giving me a secure and inspiring childhood and a strong faith in the future and for lending a helping hand countless times throughout the years – especially for taking care of our children a multitude of times.

Esko, Aarni, Akilles, Vinha and Urho for sharing my real life and all the adventures.

The studies included in this thesis were supported by a grant form Karin and Einar Ström’s Foundation, the Finnish Medical Foundation (Finska Läkaresällskapet), the Finnish Society of Angiology, the Foundation of Life and Health (Folkhälsan), the Sigrid Juselius Foundationa and the Perklén Foundation.

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